Use of Growth Factors and Cytokines to Treat Injuries Resulting from a Radiation Public Health Emergency

Authors: Horta, Zulmarie Perez, Case, Cullen M., and DiCarlo, Andrea L.

Source: Radiation Research, 192(1) : 92-97

Published By: Radiation Research Society

URL: https://doi.org/10.1667/RR15383.1

RADIATION RESEARCH **192**, 92–97 (2019)
0033-7587/19 $15.00

DOI: 10.1667/RR15383.1

COMMENTARY

Use of Growth Factors and Cytokines to Treat Injuries Resulting from a Radiation Public Health Emergency

Zulmarie Perez Horta,[a,1] Cullen M. Case, Jr.[b] and Andrea L. DiCarlo[a]

[a] *Radiation and Nuclear Countermeasures Program (RNCP), Division of Allergy, Immunology and Transplantation (DAIT), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Rockville, Maryland; and* [b] *Radiation Injury Treatment Network (RITN), Minneapolis, Minnesota*

Perez Horta, Z., Case, C. M. Jr. and DiCarlo, A. L. Use of Growth Factors and Cytokines to Treat Injuries Resulting from a Radiation Public Health Emergency. *Radiat. Res*. 192, 92–97 (2019).

In response to concerns over possible radiological or nuclear incidents, the Radiation and Nuclear Countermeasures Program within the National Institute of Allergy and Infectious Diseases (NIAID) was tasked by the U.S. Department of Health and Human Services to support development of medical countermeasures (MCM) to treat the acute and delayed injuries that can result from radiation exposure. To date, the only three drugs approved by the U.S. Food and Drug Administration for treatment of acute radiation syndrome are growth factors targeting granulocyte (Neupogen® or Neulasta®) or granulocyte and macrophage (Leukine®) hematopoietic cell lineages. Although these are currently stockpiled for deployment in response to a mass casualty scenario, these growth factors will likely be administered in a scarce-resources environment and availability may be limited. Therefore, there is growing interest in understanding the role that these growth factors play in mitigating radiation damage, to optimize their use and maximize the number of people who can be treated. For these reasons, the NIAID and the Radiation Injury Treatment Network organized a workshop to explore the use of growth factors and other cytokines as MCMs in the treatment of radiation-induced injuries. Subject matter experts from government, industry and academia gathered at this workshop to discuss the concept of operations, triage and treatment, administration to diverse civilian populations, growth factors under development for radiation indications, and how the practice of medicine can inform other potential approaches.

INTRODUCTION

To ensure the nation's preparedness in the event of a radiation public health emergency, the U.S. government has tasked several agencies to research and develop medical countermeasures (MCMs) that can be used for the treatment of radiation injuries. The Radiation and Nuclear Countermeasures Program (RNCP), within the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) is responsible for supporting early research and development activities of promising approaches that can eventually be licensed for radiation indications and included in the Strategic National Stockpile. The Radiation Injury Treatment Network (RITN), a network of medical centers across the country with bone marrow failure expertise, also plays important roles, both prior to an incident through the preparation of guidelines and training of personnel, and during the emergency by providing comprehensive care for acute radiation syndrome (ARS) patients and collecting data for retrospective analysis.

Growth factors (GFs) and cytokines have been of interest since the early stages of MCM research and development. Currently, the only three drugs approved by the U.S. Food and Drug Administration (FDA) to treat the acute radiation syndrome (ARS) are the growth factors Neupogen®, Neulasta® and Leukine®. To better understand the use of these and other growth factors and cytokines in treating radiation injuries, RNCP/NIAID and RITN convened a workshop in Rockville, MD on August 30th, 2018. The workshop focused on current clinical practice using GFs, pre-clinical approaches under development and strategic planning for MCM deployment. Invited participants included U.S. government planning and funding agencies, healthcare providers, hospital-based emergency management staff and pharmacists interested in disaster planning, as well as industry and academic researchers engaged in pre-clinical development of candidate products. Through talks and a guided discussion session, participants shared information on the government infrastructure for adminis-

[1] Address for correspondence: DAIT, NIAID, NIH, 5601 Fishers Lane, Room 7A61, Rockville, MD 20852; email: zulmarie.perezhorta@nih.gov.

tration of products during a mass casualty incident, updates on treatment approaches under development, and how physicians approach the use of growth factors and cytokines in other clinical areas (full meeting report available online at http://dx.doi.org/10.1667/RR15363.1).

BACKGROUND

Ionizing radiation can affect all tissues of the body, and although these tissues exhibit different degrees of radiosensitivity, radiation-induced multi-organ dysfunction is a hallmark of radiation injuries after exposure (*1*). Thus, the early search for mitigators for radiation-induced damage centered on finding systemic molecules capable of activating multiple cellular pathways. GFs and cytokines produced by immune cells, endothelial cells, fibroblasts and other stromal cells, bind receptors on responding cells all over the body to mediate a wide variety of cell activities. Cytokines have been widely studied for treatment of diseases such as lung (*2*) and cardiac fibrosis (*3*) and cancer (*4*). Furthermore, granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), erythropoietin (EPO) and thrombopoietin (TPO) have been used to treat victims of radiation accidents, including those of Tokai-mura, Japan (*5*), Goiania, Brazil (*6*), Fleurus, Belgium (*7*) and Dakar, Senegal (*8*).

The FDA Animal Rule (*9*) was used for the approval of filgrastim (Neupogen, 2015; Amgen®, Thousand Oaks, CA),[2] pegfilgrastim (Neulasta, 2015; Amgen)[3] and sargramostim (Leukine, 2018; Partner Therapeutics, Lexington, MA).[4] These drugs are indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic sub-syndrome of ARS, H-ARS). In addition to growth factors targeting the neutrophil and macrophage lineages, other approaches are being studied to use these molecules for the treatment of the other sub-syndromes of ARS. For this meeting, GFs and cytokines were defined as small proteins involved in cell signaling, fighting infections and inducing immune responses. Interleukins, chemokines, interferons and other products that simulate these responses (e.g., small molecule mimetics) were also included.

MEETING OVERVIEW

Session 1: Planning Overview

In determining how to better use GFs and cytokines in response to a radiological incident, it is important to understand the limitations of the emergency context in which they will be administered. For this purpose, representatives from U.S. government agencies reviewed anticipated scenarios and the current status for the use of GFs and cytokines. In the government's planned approach for an improvised nuclear device (IND) disaster, it is generally acknowledged that operations will occur under a scarce-resource setting with a limited number of treatment doses available after a radiation incident (*10*), leading healthcare providers to make difficult decisions. However, the number of casualties can be greatly decreased if the public avoids the dangerous fallout zone and follows guidance to shelter in place.

RITN perspective and growth factors working group update. The RITN[5] is a group of hospitals with cancer treatment specialty, preparing to care for ARS patients from a mass casualty radiological incident (*11*). RITN is focused on the distant community that will receive the medical surge as patients are moved across the country. In addition to providing emergency preparedness training to participating hospitals and creating referral guidelines, RITN will track and provide data on bed and cytokine availability within the participating hospitals. Patients will be categorized into radiation-only exposure or minimal trauma versus combined injury with recommendations for GF administration. Unfortunately, the determination of most patients in the radiation combined injury categories would be ''GF not indicated'', while determination of patients in the radiation-only or minimal trauma category would be ''GF indicated'' or ''GF indicated only if supply widely available''. RITN has formed a Cytokine Working Group, composed of RITN members, government staff and experts in hematology, transplant, burns and trauma, to create guidelines for management of combined injuries with growth factors, formalize collaborations with burn and trauma organizations, develop materials to support cytokine triage guidelines and discuss ethical considerations.

The RNCP/NIAID growth factors and cytokines portfolio. Since 2005, NIAID's RNCP has provided funding for research and development of many growth factor and cytokine approaches to address radiation injuries. Due to the focus of treating civilian populations, a product is considered efficacious if it leads to improved survival of at least 30% over vehicle-treated controls when administered 24 h or later after irradiation. Although more than 29 of these kinds of approaches have received NIAID support, including several presented at the meeting, of greatest importance is the RNCP-supported pre-clinical work that led to the licensure of Neupogen and Neulasta in 2015 (*12, 13*).

Global World Health Organization (WHO) consensus statement on use of cytokine therapies for ARS. In 2009, to determine if past use of GF during other radiation exposure incidents was beneficial, the WHO established a consultancy group to provide an evidence-based recommendation for clinical management of H-ARS (*7*). Using the Grading of

[2] FDA Approves Radiation Medical Countermease. (https://bit.ly/2YYB67w)

[3] Highlights of Prescribing Information. (https://bit.ly/2U8OwdE)

[4] FDA Approves Leukine for Acute Radiation Syndrome. (https://bit.ly/2IqvoXb)

[5] Radiation Injury Treatment Network (RITN). (https://ritn.net)

Recommendations, Assessment, Development, and Evaluation (GRADE) System, published reports used for recommendations had to demonstrate bone marrow failure, document cytokine(s) used, and note a treatment effect on the hematopoietic system. Taken together, the data justified a strong recommendation to administer G-CSF or GM-CSF when the measured absolute neutrophil count (ANC) is less than 0.50×10^9 cells/l. While administration of hematopoietic stem cells to overcome marrow aplasia in the absence of non-hematopoietic organ failure is recommended, the findings do not strongly support their use.

Optimizing use of G-CSF in military operations: Scenario-based modeling. In addition to civilian use, the U.S. government must also consider the stockpiling and use of drugs for soldiers who might be placed in harm's way, since military requirements for an MCM differ from those for civilian use. To address this possibility, scenario-based modeling was used to provide insight into options for optimizing the realistic use of G-CSF in military-based operations and demonstrated more flexibility in delaying initiation of treatment. The military scenario reflects the ability to use expert medical decision makers within a well-established command and control structure in a chaotic environment to receive and provide real-time inputs that can alter treatment recommendations. The use of scenario-based modeling can assist in expanding research goals, identifying opportunities to improve outcomes and help determine optimal treatment protocols and concepts of operations under the constraints and limitations of a real-world scenario.

Session 2: Pre-Licensure Research

Several MCMs under development for the treatment of the sub-syndromes of ARS were discussed, including considerations for their performance alone or in combination with ARS-approved growth factors that could be considered standard of care.

Epidermal growth factor (EGF). EGF binds and activates the EGF receptor leading to activation of pathways (*14*) that mediate many cellular activities. Bone marrow-derived HSCs express the EGF receptor in response to irradiation, and EGF has been shown to promote HSC regeneration *in vivo*. Importantly, 7 day administration of EGF initiated 24 h postirradiation increased survival by 40% (*15*), and addition of G-CSF to EGF treatment led to a further increase in survival (20% in controls, 67% in EGF, 86% in EGF with G-CSF). Furthermore, administration of EGF receptor antagonist prior to irradiation reduced survival, demonstrating that EGF receptor signaling is sufficient and necessary to mitigate radiation damage.

Fibroblast growth factor (FGF). Endogenous FGF is found in many tissues in the body, and its levels can vary dramatically. Cost restrictions associated with the use of human recombinant (hrFGF2) led to the development of FGF-P, a 17 amino acid peptide fragment of FGF2 (*16*). The FGF-P molecule has a simple synthesis process, is inexpensive and binds well in the activation site of the FGF receptor-1 (FGFR1). Notably, FGF-derived growth factors have been shown to protect the GI crypts against radiation injury in the duodenum (*17*), and SC FGF-P has been shown to improve survival in a partial-shielded, GI-ARS mouse model.

Romiplostim (Nplate®). Nplate is a fusion protein containing a peptide region to bind the TPO receptor and an Fc carrier domain to increase the half-life, which is FDA approved for the treatment of thrombocytopenia in patients with chronic immune thrombocytopenia (ITP). Published studies in mice demonstrated that when Nplate was administered for days 1, 3 or 5 after a lethal total-body irradiation (TBI), 100% of the irradiated mice survived (*18*). Recent studies conducted through NIAID/RNCP's advanced product development contract showed that a single dose of Nplate led to a 40% improvement in survival of irradiated mice at an $LD_{70/30}$ TBI model (*19*). Initial pharmacokinetics/pharmacodynamics (PK/PD) in the NHP model showed that with a radiation dose of $LD_{30/45}$, all treatment options improved the platelet nadir. Interestingly, co-administration of Nplate with G-CSF resulted in a further improvement of neutrophils in addition to the platelet response, suggesting an additive effect in NHPs for the combination treatment. This was similar to previously published studies, which demonstrated that combining human megakaryocyte growth and development factor (MGDF) with G-CSF enhanced multilineage hematopoietic recovery (*20*).

HemaMax (rHuIL-12). IL-12 has pleiotropic effects on the innate and adaptive immune cells, including stimulation of hematopoiesis. HemaMax contains a complex glycosylation structure that increases half-life allowing administration every 2–4 weeks, thus a single dose is able to elicit hematological and immune-elated effects with little toxicity. HemaMax has shown efficacy when administered at 24 and 48 h post-TBI in NHPs and mice, respectively (*21*). Compared to Neupogen, Neulasta and Leukine, the single administration of HemaMax and the restoration of all cell types in regenerating bone marrow suggests an advantage for its use in the event of a mass casualty incident.

BBT-059 (peg-IL-11). This mono-PEGylated IL-11 analog, created by binding polyethylene glycol (PEG) to the C-terminus end of the IL-11, results in an increased molecular weight, slower clearance from the body and increased potency *in vivo*. Compared to Neumega, which peaks in circulation at 1–2 h after injection and is no longer detected by 10 h, BBT-059 is absorbed slower, peaking at 24 h and lasting 2–3 days in the circulation. Studies performed in mice demonstrated that a single SC injection of BBT-059, administered 24–48 h post-TBI, increased the 30-day survival of mice by 50–60%, and in combination with G-CSF, led to even greater improvements in survival (*22*).

Session 3: Clinical Use and Practice of Medicine

Physicians with relevant experience in the areas of growth factors and cytokines discussed the current use of these treatments in the clinic and their potential use as MCMs during a radiation emergency. It was stressed that considerations for special populations, such as pediatric and geriatric victims, must also be taken into account in planning for the use of GFs and cytokines in these scenarios.

Growth factors/cytokines in transplantation. Experience from transplants in the 1980s showed that myeloablative conditioning resulted in long recovery times, while a decrease of ANC to 100 cells/μl after chemotherapy led to dramatic increases in the infection rates (*23*). It has been demonstrated that the use of G-CSF and GM-CSF has an effect on shortening neutrophil recovery in the clinic. Initially, the efficacy of G-CSF was demonstrated by an increase in the number of neutropenic patients free of fever, together with a faster time to neutrophil recovery for those who received G-CSF compared to placebo (*24*). For transplant patients, there was a 3-day improvement in median days to reach an ANC $>$500 when G-CSF was given after stem cell infusion, resulting in a lower number of in-hospital days. Meanwhile, neutrophil recovery to $>$500 and $>$1,000 cells/μl was primarily observed for transplant patients who received GM-CSF after infusion of peripheral blood, with or without bone marrow stem cells and not with bone marrow alone (*25*).

Cytokine considerations for children and other special populations. Many factors must be taken into consideration for the clinical management of radiation exposure in special populations. Differences between children and adults in hematopoiesis can contribute to toxicity and efficacy, such as location of hematopoiesis, amount of total active bone marrow dedicated to blood cell production, presence of extramedullary hematopoiesis and higher stem cell division in children. There are also many differences in pediatric versus adult pharmacokinetics, including the volume of distribution of hydrophilic and lipophilic drugs, decreased protein binding, and decreased hepatic and renal clearance in children (*26*). Dosing of G-CSF (*27*) and GM-CSF (*28*) for pediatric use is based on PK studies and efficacy. The recommended use of cytokines in children for uncomplicated exposures of $\geq$2 Gy would be similar to that for adults (filgrastim 5–10 μg/kg/day, pegfilgrastim 6 μg/kg, sargramostim 250 μg/m^2/day), with the potential addition of TPO mimetics as deemed appropriate by the treating physician.

DISCUSSION

Breakout sessions brought together all stakeholders and subject matter experts to discuss the pre-clinical model considerations, the science of cytokines, optimal clinical use, operational considerations, regulatory considerations and concepts on the horizon.

Pre-Clinical Model Considerations

To assess the efficacy of a GF/cytokine, the chosen animal model must be appropriate for the proposed mechanism of action. Other considerations include the following: gender and strain differences; impact of microbiome; ''clean vs. dirty'' facilities; medical management; selection of radiation exposure devices; and radiation dose rate. Pilot studies in the selected species and strain are highly encouraged. Due to FDA Animal Rule requirements for testing of MCMs in more than one animal model, alternatives to rodent and NHP models are actively being developed (e.g., minipigs and rabbits). Partial-body exposure and the use of outbred strains of animals should also be considered; these simulate a more realistic radiation incident, since homogeneous exposure and genetic similarities are not expected in human patients.

Science of Cytokines

The dosing and timing of GF/cytokine administration is critical. For example, evidence suggests that GFs should not be administered too far in advance of radiation exposure, since they can accelerate cell division, making cells more susceptible to radiation. Likewise, if given too early after exposure the transient increase in neutrophils that follows irradiation can lead to faster drug clearance and a shorter half-life. Meanwhile, the presence of spared bone marrow resulting from the heterogenous, non-uniform radiation exposures and the shelter-in-place guidance expected after an incident may allow for lower doses or delayed administration of GFs (*29, 30*). Preclinical studies suggest that one half of the recommended 10 μg/kg dose of G-CSF could be used, while GM-CSF might represent a treatment option if early growth factor administration is not possible, since it was shown to be efficacious 48 h postirradiation in published NHP studies (*31*). Moreover, preclinical evidence in mice suggests that fewer injections of G-CSF could have similar survival benefit (*32*), allowing for the treatment of more casualties.

Optimal Clinical Use

G-CSF is known to be non-toxic and safe to use in special populations, with few side effects and no documented long-term negative effects. Use of newer MCMs under development with potential advantages over approved drugs is still uncertain as the risks are unknown; however, these agents might enhance efficacy of GF/cytokines in complex scenarios such as mixed-field irradiations and/or radiation combined injury models. Additionally, novel approaches are needed, with additional multilineage hematopoietic and/or non-hematopoietic effects on the various sub-syndromes of ARS such as GI.

Operational Considerations

During a radiation mass casualty event, it will be crucial to categorize casualties to provide them with optimal care as

soon as possible. An important factor to consider is the level of supportive care necessary for each MCM to be efficacious. Overall, meeting participants agreed that more cooperation is needed between the U.S. government and industry to address scarce-resource situations, vendor-managed inventories and expectations for companies. A final stockpiling constraint that was considered was the limited availability of storage, and the need for approaches that work systemically, benefiting many organ systems after irradiation, such as the bone marrow, GI tract, lung, and/or myelosuppression resulting from chemical exposures.

Regulatory Considerations

Due to the nature of MCM use in emergency scenarios, the drugs developed for this indication require a primary, clinical indication, thus providing a feasible business model for the company and supporting the development costs of the drug. Another strategy to minimize cost and time of licensing a product is repurposing existing FDA-approved/licensed drugs for radiation exposure indications. The potential need for polypharmacy approaches and the impact of this complex baseline group of therapies was also discussed. In terms of MCM development, larger pre-clinical studies may be needed, to include G- or GM-CSF, now considered standard of care, as additional treatment arms in efficacy studies.

On the Horizon

Treatment of damage to other organ systems, such as the GI and lungs, continues to be an unmet need. Therefore, the development of GFs and cytokine approaches, which work through other hematopoietic lineages and support additional mechanisms of action, is important. Products that improve existing drugs and approaches by extending the half-life, decreasing effective dose, optimized formulations or more accessible routes of administration are of interest. Promising approaches include drugs used in transplants, TPO receptor agonists and anti-oxidants approved for other indications.

CONCLUSION

Growth factors and cytokines represent an important component of the preparedness strategy for treating radiation-induced injuries. Government agencies will continue to collaborate with non-government organizations, academic and industry researchers to advance these approaches for future use in case of a radiological or nuclear incident.

Received: March 12, 2019; accepted: April 10, 2019; published online: May 7, 2019

REFERENCES

1. Hall E, Giaccia A. Radiobiology for the radiologist. Philadelphia. Lippincott, Williams & Wilkins; 2006.
2. Okada T, Sugie I, Aisaka K. Effects of gamma-interferon on collagen and histamine content in bleomycin-induced lung fibrosis in rats. Lymphokine Cytokine Res 1993; 12:87–91.
3. Verma SK, Garikipati VNS, Krishnamurthy P, Schumacher SM, Grisanti LA, Cimini M, et al. Interleukin-10 inhibits bone marrow fibroblast progenitor cell-mediated cardiac fibrosis in pressure-overloaded myocardium. Circulation 2017; 136:940–53.
4. Chen C, Liu X, Ren Y. Interleukin 21 treatment in a murine model as a novel potential cytokine immunotherapy for colon cancer. Adv Clin Exp Med 2018; 27:583–9.
5. Asano S. Multi-organ involvement: lessons from the experience of one victim of the Tokai-mura criticality accident. BJR Suppl 2005; 27:9–12.
6. Brandao-Mello CE, Oliveira AR, Valverde NJ, Farina R, Cordeiro JM. Clinical and hematological aspects of 137Cs: the Goiania radiation accident. Health Phys 1991; 60:31–9.
7. Gourmelon P, Benderitter M, Bertho JM, Huet C, Gorin NC, De Revel P. European consensus on the medical management of acute radiation syndrome and analysis of the radiation accidents in Belgium and Senegal. Health Phys 2010; 98:825–32.
8. Bertho JM, Roy L, Souidi M, Benderitter M, Bey E, Racine R, et al. Initial evaluation and follow-up of acute radiation syndrome in two patients from the Dakar accident. Biomarkers 2009; 14:94–102.
9. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) Product Development Under the Animal Rule. Guidance for Industry. 2015.
10. DiCarlo AL, Maher C, Hick JL, Hanfling D, Dainiak N, Chao N, et al. Radiation injury after a nuclear detonation: medical consequences and the need for scarce resources allocation. Disaster Med Public Health Prep 2011; 5:S32–44.
11. Case C, Jr. 10 years of preparedness by the Radiation Injury Treatment Network. Curr Hematol Malig Rep 2017; 12:39–43.
12. Farese AM, Cohen MV, Katz BP, Smith CP, Gibbs A, Cohen DM, et al. Filgrastim improves survival in lethally irradiated nonhuman primates. Radiat Res 2013; 179:89–100.
13. Hankey KG, Farese AM, Blaauw EC, Gibbs AM, Smith CP, Katz BP, et al. Pegfilgrastim improves survival of lethally irradiated nonhuman primates. Radiat Res 2015; 183:643–55.
14. Herbst RS. Review of epidermal growth factor receptor biology. Int J Radiat Oncol Biol Phys 2004; 59:S21–6.
15. Doan PL, Himburg HA, Helms K, Russell JL, Fixsen E, Quarmyne M, et al. Epidermal growth factor regulates hematopoietic regeneration after radiation injury. Nat Med 2013; 19:295–304.
16. Casey-Sawicki K, Zhang M, Kim S, Zhang A, Zhang SB, Zhang Z, et al. A basic fibroblast growth factor analog for protection and mitigation against acute radiation syndromes. Health Phys 2014; 106:704–12.
17. Zhang L, Sun W, Wang J, Zhang M, Yang S, Tian Y, et al. Mitigation effect of an FGF-2 peptide on acute gastrointestinal syndrome after high-dose ionizing radiation. Int J Radiat Oncol Biol Phys 2010; 77:261–8.
18. Yamaguchi M, Hirouchi T, Yokoyama K, Nishiyama A, Murakami S, Kashiwakura I. The thrombopoietin mimetic romiplostim leads to the complete rescue of mice exposed to lethal ionizing radiation. Sci Rep 2018; 8:10659.
19. Bunin D, Bakke J, Green CE, Javitz HS, Fielden M, Chang PY. Romiplostim (Nplate(R)) as an effective radiation countermeasure to improve survival and platelet recovery in mice. Int J Radiat Biol 2019. (In press)
20. Farese AM, Hunt P, Grab LB, MacVittie TJ. Combined administration of recombinant human megakaryocyte growth and development factor and granulocyte colony-stimulating factor enhances multilineage hematopoietic reconstitution in nonhuman primates after radiation-induced marrow aplasia. J Clin Invest 1996; 97:2145–51.

21. Basile LA, Ellefson D, Gluzman-Poltorak Z, Junes-Gill K, Mar V, Mendonca S, et al. HemaMax (TM), a recombinant human Interleukin-12, is a potent mitigator of acute radiation injury in mice and non-human primates. Plos One 2012; 7:e30434.

22. Plett PA, Chua HL, Sampson CH, Katz BP, Fam CM, Anderson LJ, et al. PEGylated G-CSF (BBT-015), GM-CSF (BBT-007), and IL-11 (BBT-059) analogs enhance survival and hematopoietic cell recovery in a mouse model of the hematopoietic syndrome of the acute radiation syndrome. Health Phys 2014; 106:7–20.

23. Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 1966; 64:328–40.

24. Welte K, Gabrilove J, Bronchud MH, Platzer E, Morstyn G. Filgrastim (r-metHuG-CSF): the first 10 years. Blood 1996; 88:1907–29.

25. Advani R, Chao NJ, Horning SJ, Blume KG, Ahn DK, Lamborn KR, et al. Granulocyte-macrophage colony-stimulating factor (GM-CSF) as an adjunct to autologous hemopoietic stem cell transplantation for lymphoma. Ann Intern Med 1992; 116:183–9.

26. Lu H, Rosenbaum S. Developmental pharmacokinetics in pediatric populations. J Pediatr Pharmacol Ther 2014; 19:262–76.

27. Stute N, Santana VM, Rodman JH, Schell MJ, Ihle JN, Evans WE. Pharmacokinetics of subcutaneous recombinant human granulocyte colony-stimulating factor in children. Blood 1992; 79:2849–54.

28. Stute N, Furman WL, Schell M, Evans WE. Pharmacokinetics of recombinant human granulocyte-macrophage colony-stimulating factor in children after intravenous and subcutaneous administration. J Pharm Sci 1995; 84:824–8.

29. MacVittie TJ, Bennett AW, Farese AM, Taylor-Howell C, Smith CP, Gibbs AM, et al. The effect of radiation dose and variation in Neupogen(R) initiation schedule on the mitigation of myelosuppression during the concomitant GI-ARS and H-ARS in a nonhuman primate model of high-dose exposure with marrow sparing. Health Phys 2015; 109:427–39.

30. Farese AM, Bennett AW, Gibbs AM, Hankey KG, Prado K, Jackson W 3rd, et al. Efficacy of Neulasta or Neupogen on H-ARS and GI-ARS mortality and hematopoietic recovery in nonhuman primates after 10-Gy irradiation with 2.5% bone marrow sparing. Health Phys 2019; 116:339–53.

31. Clayton NP, Charpentier EJJ, LaCasse ER, Khan-Malek RC, Keutzer JM. Sargramostim accelerates leukocyte recovery and improves mortality rate at day 60 in a non-human primate model of hematopoietic acute radiation syndrome when administered 48 h after total body irradiation. Blood 2016; 128:2512.

32. Satyamitra M, Kumar VP, Biswas S, Cary L, Dickson L, Venkataraman S, et al. Impact of abbreviated filgrastim schedule on survival and hematopoietic recovery after irradiation in four mouse strains with different radiosensitivity. Radiat Res 2017; 187:659–71.