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COMMENTARY

Development and Licensure of Medical Countermeasures for Platelet Regeneration after Radiation Exposure

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INTRODUCTION

The Department of Health and Human Services (HHS) is charged with protecting civilian populations by providing leadership in research, development, acquisition, deployment and use of effective medical countermeasures (MCMs) for treatment of injuries resulting from a radiological/nuclear incident. HHS has assigned the National Institute of Allergy and Infectious Diseases (NIAID) to develop and implement a research and development agenda (*1*). After unintentional radiation exposure in the hematopoietic dose range (~2 Gy to 8 Gy), potentially life-threatening neutropenia and thrombocytopenia can result, increasing the risk of death due to opportunistic infections and/or hemorrhage (*2*). Although both conditions are likely to be major contributors to mortality in untreated individuals, little recent work had been done to develop drugs to enhance platelet counts after irradiation, and there are currently no licensed therapeutics (other than blood products) in the Strategic National Stockpile for treatment of this radiation-induced complication. To address this aspect of radiation damage, NIAID funded a portfolio of grants in late 2008 to develop MCMs to mitigate/treat radiation-induced thrombocytopenia and enhance survival. Supported research includes studies designed to generate data that would be required by the U.S. Food and Drug Administration (FDA) for licensure of an MCM as a mitigator of radiation-induced thrombocytopenia (RIT). The NIAID Radiation Countermeasures Program held a workshop on March 22–23, 2010 to bring together representatives from U.S. Government (USG) agencies with researchers who are developing MCMs and animal models to evaluate approaches to enhance regeneration of platelets after radiation exposure [(*3*); available online at http://dx.doi.org/10.1667/RROL01.1]. The main goal of the discussion session that followed the science presentations was to clarify issues regarding potential paths forward for FDA licensure of products for a hematopoietic, acute radiation syndrome (ARS) indication and encourage discussion about the challenges involved in development of NIAID-funded (and other) MCMs to minimize thrombocytopenia and enhance survival after unintentional radiation exposure.

After irradiation, megakaryocytes, which give rise to platelets, migrate to the osteoblastic niche (*4*). Megakaryocytes in the circulation are known to be more radioresistant to radiation than other bone marrow-derived cells; however, their progenitor populations appear to be more radiosensitive (*5*). Depending on the degree of radiation damage, a drop in platelet count can be observed in less than a week (*6*), with the risk of life-threatening bleeding increased as the level of circulating platelets drops below 20,000/mm^3. In small accidents, supportive transfusion will be part of medical management; however, logistical requirements to provide care to large numbers of victims after a mass casualty incident are great, and emergency preparedness experts believe that an effective pharmacological therapy that mitigates or treats radiation-induced thrombocytopenia would offer dramatic advantages. Thus preferred drugs are those that can be easily administered (e.g. oral, subcutaneous, intramuscular routes of delivery) with low toxicity. Although some drugs are currently in development to treat RIT after cancer radiotherapy, they are often administered as radioprotectors – in advance of the radiation exposure. Due to the challenges involved in providing MCMs in the wake of a mass casualty incident, treatments are not expected to be available until least 24 h after an event, so drugs that are effective at this time postexposure (and beyond) are the most desirable.

Animal Models and Development of Mitigators for RIT

Licensing pathways provided by the FDA under 21 CFR Parts 314 subpart I and 601 subpart H (referred to

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as the FDA Animal Rule) as well as those outlined within the 2009 FDA draft guidance on FDA Animal Rule model development (*7*) are most likely to be used in the licensing of any MCM for mitigation of injury from exposure to lethal radiation. Therefore, it is critical that appropriate animal models be developed and validated for their ability to reflect injuries caused by radiation exposure to the hematopoietic compartment in humans. A number of models are currently under development to study radiation-induced bone marrow damage and document the efficacy of new MCMs (*8*). An important component of the testing of treatments for hematopoietic ARS is animal supportive care, in which infection and hemorrhage are treated, and which also includes replacement of lost fluids and nutrient support. Technological advances and availability of improved supportive care for larger animals [i.e. dogs and non-human primates (NHPs)] has led to the need to re-establish mortality curves across a range of radiation exposures to test MCMs in a model that mimics how they would likely be used clinically. Therefore, researchers are developing updated canine and NHP models of total-body irradiation with supportive care (intravenous fluids, targeted antibiotics and blood products) for hematopoietic ARS. The historical dose modification factor for basic support is ~1.3 in dogs (*8*) and ~1.2 in NHPs.[2]

There is considerable historical evidence that the administration of thrombopoietin (TPO) or megakaryocyte growth and development factor (MGDF – a truncated form of TPO) yields a survival benefit in irradiated animals. For example, recombinant forms of TPO have been shown to increase platelet counts and/or improve survival after total-body radiation exposure in small and large animal models (*10–14*). However, findings of the induction of autoantibodies after administration of MGDF, which led to severe thrombocytopenia in some healthy controls, resulted in the halting of MGDF's clinical development for chemotherapy-induced thrombocytopenia (CIT) (*15, 16*). This led to the discontinuation of U.S. clinical trials for the full-length TPO as well. Nonetheless, clinical development of TPO continued outside of the United States, and a human recombinant TPO molecule (designated TPIAO) is currently licensed in China for the treatment of chemotherapy-induced thrombocytopenia. The package insert for TPIAO describes early studies demonstrating its efficacy in irradiated NHPs. Several companies have since developed small molecule treatment approaches, targeting binding sites on the TPO receptor. Two of these drugs, Nplate® (a peptide mimetic from Amgen) and Promacta® (a non-peptide mimetic from Glaxo SmithKline), are now FDA-licensed in the United States to treat idiopathic thrombocytopenic purpura. Because these drugs are already licensed or in trials for other diseases, information that might be required for a drug label extension for radiation-induced thrombocytopenia may already be available [e.g. safety, toxicity, pharmacodynamics (PD) and pharmacokinetics (PK)]. Although this makes them attractive drugs for testing as radiation MCMs, the species specificity of some of these small molecule drugs complicates their development via the FDA Animal Rule pathway. For example, Promacta®, a non-peptide mimetic, shows activity only in humans and chimpanzees (*17*). Nonetheless, this drug is now being evaluated in a radiation exposure model and shows promise in its ability to enhance megakaryopoiesis.[3] Although Nplate®, a peptide mimetic, showed early promise in a preclinical model of chemo/radiotherapy-induced thrombocytopenia,[4] follow-on studies with radiation exposures alone have not been published. These and other potential TPO mimetic approaches are fully described elsewhere (*18*).

Some MCM development for RIT focuses on the bone marrow stroma and the impact of vascular endothelial cells and pro-angiogenic factors on platelets and survival after radiation exposure. In addition to the role that vascular growth factors play in enhancing bone marrow recovery, other stromal elements also appear to play a role in megakaryocytic recovery after irradiation. For example, parathyroid hormone, currently licensed and in clinical use for osteoporosis (Eli Lilly, Forteo®), increases platelet counts and survival when administered after irradiation (*19*). Bone marrow-targeted cell therapies are also being pursued as treatments for radiation-induced thrombocytopenia, including *ex vivo* expanded megakaryocyte progenitors. Other novel approaches currently funded by NIAID to mitigate RIT include:

- Angiotensin (1–7) – increases progenitor cell recovery (*20*) and reduces severity of thrombocytopenia when given after total-body irradiation in mice.
- Homspera – a formulation of the synthetic peptide analog of Substance P that mitigates radiation injury to the megakaryocyte lineage.
- Anti-PF4 antibodies – released during platelet activation, PF4 plays a role in megakaryopoiesis (*21*). Blocking PF4 binding on the megakaryocyte enhances proliferation.

[2] A. M. Farese *et al.,* Medical management alone increases survival of lethally irradiated nonhuman primates within the hematopoietic syndrome. Presented at the 54th Annual Meeting of the Radiation Research Society, 2008.

[3] Y. Chen *et al.,* Eltrombopag enhances megakaryopoiesis of human bone marrow in 3D bioreactors after radiation exposure. Presented at the 56th Annual Meeting of the Radiation Research Society, 2010.

[4] C. Hartley *et al.,* The novel thrombopoietic agent AMG 531 is effective in pre-clinical models of chemo/radiotherapy induced thrombocytopenia. Presented at the Annual Meeting of the American Association for Cancer Research, 2005.

- Octadecenyl thiophosphate – a lyso-phosphatidic acid analog that enhances platelet counts and increases survival in a mouse model of radiation exposure (*22*).
- CBLB502 – a flagellin-derived, toll-like receptor 5 agonist that activates NFkB, resulting in increased platelet levels, and improved survival in irradiated NHPs (*23*).

Regulatory and Funding Issues for Development and Licensure of MCMs for RIT

The four pillars of the FDA Animal Rule include requirements that must be met to give FDA confidence in MCM efficacy data obtained from animal studies: (1) demonstration of a reasonably well-understood pathophysiological mechanism for the toxicity caused by the radiation exposure and its mitigation by the MCM in animals and humans; (2) efficacy in at least one (usually more than one) well-characterized animal species, predictive for humans; (3) use of an animal efficacy study end point that is clearly related to the desired benefit in humans, usually prevention of mortality or major morbidity; and (4) availability of sufficient human and animal PK and PD to allow for selection of a human dose. Pivotal animal efficacy protocols should clearly delineate the concomitant medical management regimen (including timing of administration of the drug and clinically relevant triggers to initiate administration) to be used in the study. Considerable thought should be put into the development of radiation protocols that simulate terrorist or mass casualty incident scenarios, because experiments that have clinical relevance for radiotherapy are not necessarily appropriate for a radiation counterterrorism indication.

Cell therapy approaches face additional, unique challenges, in that the human cells are the "drug product" that must be licensed by the FDA, and the product tested in animals for efficacy must be identical to the product to be used in humans. Because human cells may not function in the same way in an animal as they would in humans, administration of a homologous animal cell preparation in an animal model may need to be considered and discussed with the FDA.

Jurisdiction over small molecule or protein MCMs for RIT rests within FDA's Division of Medical Imaging Products in the Office of Oncology Drug Products within the Center for Drug Evaluation and Research (CDER). For these drug products, initial contact should be made with FDA's Office of Counter-Terrorism and Emergency Coordination (OCTEC) within CDER. Although OCTEC is not a review division, this liaison group can provide guidance on the licensure of radiation MCMs. Approaches involving cell therapies or some biologics would be received by FDA's Center for Biologics Evaluation and Research (CBER). For these MCMs, applicants should contact the Senior Advisor for Counterterrorism/Medical Countermeasures, Office of the Director, CBER. These FDA liaison groups can provide potential MCM sponsors with important guidance regarding licensure. Because there is an urgency to develop safe and effective drugs for this indication, groups should meet with the FDA early for guidance.

Funding of MCM candidate product development for ARS includes development of novel strategies and partnerships with the USG to fund advanced development. USG agencies, with roles ranging from strategic partner/investor to eventual customer for a fully licensed MCM, must ensure optimal use of funds. It is clear that government funding in this area is advancing the development of MCMs for RIT; continued collaborations between researchers developing pro-platelet approaches and USG funding, licensure and procurement agencies is critical and should accelerate the development and licensure of drugs to treat thrombocytopenia and increase survival in radiation-exposed individuals.

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