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MEETING COMMENTARY

A Poly-Pharmacy Approach to Mitigate Acute Radiation Syndrome (ARS)

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INTRODUCTION

The pathophysiology of radiation-induced injuries is complex and can manifest as multiorgan dysfunction. The resultant subsyndromes of acute radiation syndrome (ARS) and delayed effects of acute radiation exposure (DEARE) are further complicated by concurrent trauma such as burns, open wounds, fractures, and biological variables such as sex, age, preexisting conditions and dietary status. In preparing the nation to respond to a large-scale nuclear incident, it is simplistic to expect that a single medical countermeasure (MCM) will ameliorate systemic damage and lethality. Therefore, it is reasonable to envision a poly-pharmacy approach, where multiple MCMs as well as supportive care measures are deployed in treating individuals exposed to a radiological/nuclear event.

Here, the term poly-pharmacy is defined as the use of multiple drugs that are medically necessary (*1*). To date, four radiation MCMs, Neupogen®, Neulasta®, Leukine® and Nplate®, have been approved by the U.S. Food and Drug Administration (FDA) to treat ARS; however, each of these MCMs was approved individually, and not as poly-pharmaceuticals. Given the obvious need for a poly-pharmacy approach to mitigate multiorgan injuries, on October 25th, 2018, the National Institute of Allergy and Infectious Diseases (NIAID), Radiation and Nuclear Countermeasures Program (RNCP) conducted a workshop entitled, ''A Poly-Pharmacy Approach to Mitigate Acute Radiation Syndrome.'' The workshop focused on U.S. Government operational logistics for MCM deployment, the natural history of radiation-induced injuries in animal models, the current state of the science in poly-pharmacy research, and regulatory considerations for advancing these approaches. Participants included U.S. Government emergency preparedness planning and funding agencies, as well as industry partners and academic researchers involved in developing radiation MCMs. Through expert talks and guided discussions, the importance of understanding the availability and deployment of resources from the Strategic National Stockpile (SNS), drug-drug interactions between MCMs in the SNS and routinely prescribed medications, and the effect of poly-pharmacy approaches on immune-compromised populations were highlighted (full meeting report available online). While this commentary summarizes key points from the talks and discussion, it is not a review of all poly-pharmacy approaches in this field. While poly-pharmacy research is important, equally, the response to a radiological disaster entailing deployment of the SNS resources, and regulatory processes for advancement of poly-pharmacy approaches must be considered by drug developers for a successful outcome.

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MEETING PROGRAM OVERVIEW

Response and Planning Considerations

Successful disaster preparedness and response is contingent upon an understanding of the characteristics and limitations of the anticipated operational environment. A mass casualty, improvised nuclear device (IND) incident requires efficient management of resources in an environment where treatment needs will likely exceed the availability of medical resources (*2*) and disruption in travel and communication is inevitable due to destruction of infrastructure (*3*). Furthermore, complex injuries including radiation alone, physical (e.g., wounds and burns), and radiation combined injuries (RCI) that are dose-dependent will manifest at different times after exposure. Under these circumstances, poly-pharmacy approaches may be desired, but potentially not deployed due to shortages and scarcity of resources.

The U.S. Department of Health and Human Services' (HHS) Radiation Emergency Medical Management (REMM) website (www.remm.nlm.gov) is a valuable resource that provides clinicians with tools to assess and treat patients exposed to radiation. Another resource, the Radiation Triage, Treat, and Transport System (RTR), provides operational management of triage, transportation and treatment after a nuclear detonation (*4*). RTR centers transport people from ''ground zero'' to assembly areas,

then to medical facilities, and finally, to evacuation centers. Serial triaging would be based on the mass casualty triage method known as sort, assess, life-saving intervention, treatment/transport (SALT), while also taking into account resource availability (*5, 6*). Logistics for contingency standard-of-care plans should allow for substitute treatment options under scarce resource conditions and plans to co-locate these resources to maximize availability. The ethical principles for triage were developed based on patient-based (e.g., medical conditions, comorbidities, special populations, urgency for the response) and condition-based (e.g., efficacy of interventions, resource requirement, available resources) characteristics (*7*) to sort patients into immediate, delayed, minimal or expectant treatment categories. It is anticipated that these designations could evolve with changing resources and conditions (*8*). A combination of physical radiation dose (a traceable radiation dose on a physical target) and biological dose (biodose; a biological response of an organism to the absorbed dose) is crucial for triage decisions. The distance of an individual from the center of impact can determine the physical radiation dose, while biodose requires biodosimetry tests such as the cytogenetic dicentric chromosome assay (DCA).With this information in hand, both ''doses'' are evaluated in conjunction with available resources to inform treatment strategy (*9*). Biodosimetry technologies, including ''omics'', are constantly advancing and re-strategizing to anticipate limited sample availability, shortened processing times needed to suit the operational environment, and the biokinetic changes over time after exposure. For instance, researchers from the National Cancer Institute (NCI) have created an integrated approach using mRNA, miRNA and lncRNA for triage based on when the nucleic acid signature enters into circulation; therefore, these biomarkers could serve to inform about organ-specific injuries over time (*10*). Another approach, the MEdical TREatment ProtocOLs for Radiation Accident Victims (METREPOL) tool, focuses on symptomology rather than radiation dose to guide medical management (*11*).

The U.S. Strategic National Stockpile (SNS), Support for the Response to a Nuclear Incident

Created in 1999 to serve as the U.S. Government's largest supply of pharmaceuticals and medical supplies for use during a public health emergency arising from chemical, biological, radiological, nuclear and explosive (CBRNE) threats (*12*), the SNS was formerly administered by the U.S. Centers for Disease Control and Prevention (CDC), but is currently overseen by the Office of the Assistant Secretary for Preparedness and Response (ASPR) within HHS. The SNS comprises a $7B portfolio, including antibiotics, medical supplies, antidotes, antitoxins, antivirals, vaccines, and other pharmaceuticals maintained through a network of repositories and commercial partnerships for storage, maintenance and rapid transport of material. The SNS has been deployed during the 9/11 terrorist and subsequent anthrax attacks in 2001, for hurricane and monthly exercises, and more recently for the COVID-19 pandemic.

The SNS of multiple radiological/nuclear MCMs reflects the need for a poly-pharmacy approach to treat radiation injury. The SNS currently holds radionuclide decorporation agents, two granulocyte-colony stimulating factors (G-CSF, Neupogen; pegylated G-CSF, Neulasta), and a granulocyte-macrophage colony-stimulating factor (GM-CSF, Leukine). Furthermore, the SNS maintains other products with relevance to a radiation incident, such as anti-nausea drugs (ondansetron), pain medications, antibiotics, antivirals, antifungals, general pharmaceutical and medical supplies for blast and burns, electrolyte replacement, eye, and wound care. Given the arsenal of treatment options for a poly-pharmacy approach, clear instructions for use and drug-drug contraindications must be considered.

Transportation of medical material from the SNS to designated areas for distribution and dispensing requires a seamless delivery platform and concerted coordination with state and local authorities. Initially, a tiered structure would be employed involving transportation of medical supplies from the SNS to state-identified primary and secondary receipt, stage, and store (RSS) sites, or alternate remote staging sites, using commercial transportation within 24 h of declaration of the emergency. Once deployed to the states, these materials are then subject to local procedures, policies and resources for distribution and integration into the healthcare system. Identifying local sites, creating pipelines and validating material distribution are contingent upon detailed planning and coordination between the SNS and local authorities. States are funded via public health preparedness initiatives to establish and verify all-hazards public health response plans, to include multiple distribution sites, transportation details and dispensing of materials from the SNS to patients. In addition, the SNS also makes use of vendor-managed inventory (VMI) programs for distribution and coordination, where the burden of maintaining and distributing medical materials lies with the vendors. It is important to acknowledge that delivery timelines for handoff of the material to local authorities from the VMI can be expected to be longer. Another aspect of deployment is the ''push model'' for material distribution, where general medical materials will be deployed at the beginning of an emergency response without waiting for specific requests from hospitals and/or local jurisdictions because communications may be disrupted and a large number of mass casualties is assumed. This scenario underscores the importance of understanding how SNS therapeutics complement or interfere with one another, since effective treatment will likely require poly-pharmaceutical approaches from the SNS.

Given that state and local response strategies for radiation and nuclear emergencies are less mature than for biological threat scenarios, the states can streamline resource sharing by focusing on common emergency issues, such as limited

access to the impacted area, and the impaired ability to mobilize material and people. Mature strategies for emergencies (such as anthrax) can be leveraged for radiation injury. The ASPR continues to analyze and strategize these approaches to better prepare the nation to respond to public health emergencies.

Natural History of Disease

To develop a suitable poly-pharmacy regimen for treatment of multiorgan injuries after radiation exposure, it is important to understand the natural history of radiation-injuries in organ systems in at least one (generally believed to be two) well characterized animal model to meet the U.S. FDA Animal Rule licensure requirement (21 CFR 314.600-650 for drugs; 21 CFR 601.90-95 for biologics).

In a total-body irradiation (TBI) mouse model, acute lethality results from destruction of the bone marrow leading to a compromised immune system, hemorrhage and infection within 30 days postirradiation (*13*). Survivors of lethal irradiation present with residual damage weeks or months postirradiation, characterized by injuries to multiple organs, especially the hematopoietic tissue. Blood from irradiated mice demonstrates significant reduction in circulating lymphocytes, neutrophils and platelets compared to age-matched, nonirradiated mice (*14*). Other tissue dysfunction can include development of thymic lymphoma, reduction in lean muscle mass gain, fibrosis/collagen deposition in heart, lung and kidney (*15*), increase in anxious behavior and shortened lifespan. For these reasons, poly-pharmacy is needed to treat radiation-induced multiple morbidities.

The nonhuman primate (NHP) model for testing efficacy of MCMs provides a two-fold benefit: 1. It allows for demonstration of MCM efficacy; and 2. Many of the standard of care treatments provided to NHPs would be similar to those anticipated for radiation exposure victims. In this preclinical, large animal model, antibiotic, antiviral, antifungal, anti-pyretic, anti-diarrheal and anti-emetic agents are administered as a continuum of care based on a pre-established trigger-to-treat plan (*16*). NHPs also receive fluids, nutritional support and blood products, as described in the recommendations from a SNS Radiation Working Group for Medical Management of Radiation Victims (*17*), which includes administration of growth factors (GFs) and stem cell transplant, if needed. Therefore, new MCM development plans seeking FDA approval for the ARS indication should include leukocyte GFs as part of a medical management regimen. Drug developers are encouraged to conduct proof-of-concept studies using their MCM of choice and GFs in preliminary rodent studies, and to validate this approach in NHP irradiation models such as H-ARS, gastrointestinal (GI)-ARS or lung-, kidney-, heart-DEARE.

While no poly-pharmacy growth factor approaches have been FDA approved for treatment of radiation exposure victims, studies in irradiated NHP models indicate a potential for enhanced efficacy of combined GFs on survival and restoration of circulating blood indices. For example, accelerated platelet recovery in NHPs has been observed after administration of recombinant megakaryocyte growth and development factor (MGDF, a truncated form of thrombopoietin), with and without G-CSF (*18*).

An important resource to study the delayed effects of acute radiation exposure in NHPs is the NIAID-supported Radiation Survivor Cohort, located at the Wake Forest School of Medicine (WFSM, Winston-Salem, NC). This cohort consists of NHPs from various academic and U.S. Government institutions (e.g., University of Maryland at Baltimore, Armed Forces Radiobiology Research Institute and University of Illinois, Chicago) that survived TBI doses (6.5 to 8.4 Gy) and are being maintained for years to monitor late effects. WFSM combines daily observation of NHPs with detailed annual monitoring of hematology and blood chemistry, urinalysis, kidney, liver and cardiac tests, gastrointestinal, metabolic, nervous and respiratory function tests, and CT scans.

Emerging data demonstrate development of multiorgan injury in the irradiated cohorts, as a function of radiation dose, and these range from metabolic issues to immune dysfunction and multiorgan fibrosis. Irradiated NHPs develop type 2 diabetes (*19*), and these metabolic changes are linked to radiation-induced muscle fibrosis and extracellular matrix remodeling (*20*). In addition, cardiovascular issues (e.g., myocardial degeneration and fibrosis), systemic inflammation (*21*), cognitive deficits characterized by white-matter neuroinflammation, T-cell activation, increased expression of complement factors (*22*), immune dysfunction, reduced lymphocyte counts, and blind spots in the immunological repertoire have been reported in these irradiated NHPs. These data, in conjunction with studies on the atomic bomb survivors, demonstrate the need for poly-pharmacy medical management.

Poly-Pharmacy Approaches to Mitigate Radiation Injury

Most poly-pharmacy data have been generated in rodent models. One potential approach for the treatment of H-ARS uses three GF analogs: 1. BBT-015, a PEG-G-CSF analog (neutrophil stimulator); 2. BBT-007, a PEG-GM-CSF analog (white blood cell stimulator); and 3. BBT-059, a PEG-IL-11 analog (a platelet stimulator). Each has a different mechanism of action and stimulates distinct intracellular pathways. The additive effects of combining the three pegylated GFs (PEG-HGF) was demonstrated in irradiated C57BL/6 male and female mice, where optimum survival was observed with the PEG-HGF triple combination. Moreover, the PEG-HGF triple combination was as effective when administered at 1/10th the dose of a standard dose, which may have significant implications for increased safety margins and drug costs.

Other drugs such as angiotensin converting enzyme (ACE) inhibitors, that are FDA-approved to treat hyperten-

sion and cardiac disease, are also being developed for ARS. In fact, ACE inhibitors (captopril, enalapril, ramipril, fosinopril and lisinopril) were able to address multiple sequelae for both H-ARS and for DEARE (e.g., lung and kidney injury) when administered as late as 7 or 35 days postirradiation (*23*). Lisinopril, which has a long history of safety and efficacy in humans, has also been shown to augment the efficacy of the PEG-HGF triple combination in TBI H-ARS and rat PBI DEARE models. Addition of lisinopril provided an increased survival advantage in females, but no added benefit was observed in male mice.

Poly-Pharmacy Approach in a Radiation Combined Injury (RCI) Model

Combined injuries, such as cuts and burns, can exacerbate the consequences of radiation exposure (*24, 25*). In mice, the addition of punch wound trauma in irradiated animals delayed wound healing, reduced survival, and significantly increased biomarkers of tissue damage and inflammation. Several poly-pharmacy combinations have been tested in the mouse RCI model. The combination of Neulasta and ALXN4100, a thrombopoietin receptor agonist, showed improvement in 30-day survival, bone marrow recovery and weight loss, but not wound healing in the RCI group (*26*). Ghrelin, known as the hunger hormone, in combination with Neulasta, also increased survival, blood indices, bone marrow and GI cellularity in the radiation alone treatment group, but not in the RCI group. In another combination study, ciprofloxacin, a fluoroquinolone antibiotic, was tested in combination with Neulasta, and this poly-pharmacy approach significantly improved survival in the radiation alone treatment group but not in the RCI group.

Overall, these efforts show that combined injury leads to a more severe medical condition, thus it is necessary to examine approved and novel MCMs to understand their usefulness under different conditions. Given the complexity of RCI, investigators should consider testing combination or poly-pharmacy approaches that target the distinct disease pathologies, as a way to find a useful treatment for this scenario.

Regulatory Considerations

As MCMs are being developed under the U.S. FDA Animal Rule (*27*), it is important to understand what is required for approval. More importantly, if multiple MCMs are developed that could potentially be used in a poly-pharmacy approach, clarity is needed regarding the regulations for use of the combination. Is the onus on the drug developer to show a benefit or contraindication between a new MCM and existing SNS MCMs? Finally, the products under consideration for combined use might be manufactured by different companies, adding to the complexity.

There are three Acts that facilitate emergency use and deployment of medical materials in the event of a radiation public health emergency: The Public Readiness and Emergency Preparedness (PREP) Act, the Project BioShield Act of 2004, and the Pandemic and All-Hazards Preparedness Reauthorization Act (PAHPRA). Furthermore, the FDA is responsible for ensuring the quality, safety and efficacy of the drugs, biologics and medical devices, including both FDA-approved MCMs and investigational new drugs (IND), in the SNS. In 2018, oversight of the SNS was transferred to HHS/ASPR from HHS/CDC.[2]

These funding, approval and stockpiling mechanisms provide a roadmap for the eventual use of a poly-pharmacy approach. Under emergency conditions, the FDA will review existing, supportive data for the use of a poly-pharmacy approach to ensure public safety, timely approval and efficient utilization of the MCMs. An expanded-access IND application is required for stockpiling of investigational MCMs in the SNS for emergency use and post-marketing studies, as well as MCM evaluation during and after an incident (*28*). Precedents for such an approach lie in the approval for use of the anthrax vaccine, or tecovirimat (TPOXX) for the treatment of smallpox for post-exposure prophylaxis in children, despite limited pediatric data.[3]

During the drug development of an MCM under the Animal Rule, the U.S. FDA Center for Drug Evaluation and Research (CDER), Division of Imaging and Radiation Medicine, recommends that product developers and funding partners meet early and often with the agency (*27*). Constant communication is needed to reach a consensus on the key objectives of any development program, including the design of adequate and well-controlled animal efficacy studies intended to provide substantial evidence of the efficacy of the drug. It is also recommended to begin development with the end goal in mind, and consider the conditions under which the product would be used. Accordingly, for poly-pharmacy approaches, the same rules apply, and experimental design should consider and support the end-use scenario. Furthermore, clinical pharmacology studies that address drug-drug interactions must be taken into account, especially in the case of poly-pharmacy use.

CONCLUSIONS

After a radiological or nuclear incident, chances are high that individuals will suffer from multiorgan or combined injuries (*29*). A poly-pharmacy MCM approach may help strengthen the mitigation of a variety of injuries by targeting different mechanisms, pathways, and/or organ systems (e.g., vascular damage, cell loss, inflammation, oxidative stress, cell signaling), resulting in an improved overall survival or reduction in major morbidities (*30*). The research presented here supports the notion that drug combinations can

[2] https://bit.ly/3xM27vO.
[3] https://bit.ly/35Je2yk.

improve health outcomes, as demonstrated by the use of the PEG-HGF triple combo plus lisinopril or Neulasta with ciprofloxicin. These approaches highlight the fact that a combination of MCMs acting on multiple biological pathways or on different organ systems can be more effective in improving survival after lethal irradiation than a single MCM. In fact, combined GFs were shown to be effective at a lower dose, which can potentially lessen side effects and reduce drug costs. The years of radiation research funded by NIAID have shed light on the complexity of a radiation and combined injury scenario, and will continue to do so. This information suggests that a poly-pharmacy approach may be needed to mitigate such a complex injury. Clearly, more research is still needed to determine the best poly-pharmacy approaches and also to assess any drug-drug interactions.

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