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Linking the Human Response to Unplanned Radiation and Treatment to the Nonhuman Primate Response to Controlled Radiation and Treatment

Harald Dörr, Andreas Lamkowski, Dieter H. Graessle, Alexander Bennett^{}, Alla Shapiro^{*}, Ann M. Farese^{**}, Michael Garofalo^{**}, Thomas J. MacVittie^{**}, and Viktor Meineke**
Bundeswehr Institute of Radiobiology affiliated to the University of Ulm, Munich, Germany

^{*} U.S. Food and Drug Administration (FDA), Silver Spring, MD

^{**} University of Maryland, School of Medicine, Dept. of Radiation Oncology, Baltimore, MD, USA

Abstract

A key difficulty in developing countermeasures against radiation-induced health impairments is the clear lack of controlled clinical studies, due to the relatively low number of radiation victims worldwide. Instead, established and accepted animal models, as well as the recommendations of national and international expert panels and committees, are the main sources of information. Therefore, the development of countermeasures requires comparison of data from many sources and accumulation of information consistent with the U. S. Food and Drug Administration's "Animal Rule."

A new approach is the comparative analysis of human data from the SEARCH (System for Evaluation and Archiving of Radiation Accidents based on Case Histories) database and data from non-human primate (NHP) animal model studies. The SEARCH database contains 824 clinical cases from 81 radiation accidents in 19 countries. This exceptional collection of clinical data from accidentally radiation exposed persons is analysed regarding clinical signs and symptoms of radiation induced health impairments.

To analyze the time course of radiation syndromes, clinical parameters common to the SEARCH and NHP databases have to be assigned into comparable categories of clinical severity for each species. The goal is to establish a method for comparison of human and NHP data, to validate the NHP data as a surrogate for human efficacy/clinical studies and opening a way for the extraction of diagnostic and treatment methods for humans after radiation exposure according to relevant regulations.

Keywords

SEARCH database; non-human primate animal model; FDA animal rule; acute radiation syndrome

Dr. Harald Dörr Bundeswehr Institute of Radiobiology affiliated to the University of Ulm Neuherbergstr. 11 80937 Munich Germany Tel.: +49 89 3168 2260 Fax: +49 89 3168 2255 haralddoerr@bundeswehr.org.

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Introduction

Because of the affection of all stem cells and stem cell pools of the organism in the case of acute whole-body exposure, multi-organ involvement might occur and can even lead to multi-organ failure. In the clinical management of patients exposed to severe levels of ionizing radiation and suffering from acute radiation syndrome (ARS), therapeutic efforts have to be made to overcome the hematopoietic (H)-ARS, but also to address multi-organ involvement.

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Database SEARCH

The development of the database system SEARCH started with the "Moscow-Ulm Radiation Accident Database" (MURAD), which contained case histories of radiation accident victims of the Chernobyl accident. After that, an "International Computer Database for Radiation Exposure Case Histories" was created to include all available clinical data from radiation accident victims. Clinical data from radiation accidents from all over the world were then incorporated into the database system, from the beginning of nuclear technology until today.

Today, the SEARCH database contains 824 clinical cases from 81 radiation accidents in 19 countries (Friesseke et al. 2000). This exceptional collection of clinical data from accidentally radiation exposed persons allows detailed analysis of the time course, prognostic factors, and multi-organ interactions of the ARS, but also analysis of the efficacy of different therapeutic strategies.

The goal is to include data from new radiation accidents and to fill gaps in the data of already (in SEARCH) recorded cases.

SEARCH was used to develop the METREPOL system (Medical Treatment Protocols for Radiation Accident Victims), which was an entirely new approach to managing radiation accident victims on the basis of indicators of effect and repair, taking into consideration multi-organ involvement and potential treatment options (Flidner et al. 2001).

NHP Model

Well-characterized and validated animal models are needed to develop medical countermeasures for the treatment of the ARS in radiation accident victims, since there is a lack of controlled clinical studies in this area. These models must be in line with the criteria of the U.S. Food and Drug Administration's Animal Rule.

The NHP is very well-suited to model the most important acute and delayed radiation syndromes, which are the H-ARS, the gastrointestinal (GI)-ARS, and radiation-induced lung injury.

In the rhesus macaque model, the dose response relationship and time course of acute H-ARS and GI-ARS morbidity and mortality following total body irradiation (TBI) are well-defined (Farese et al 2012; MacVittie et al. 2012).

This model using rhesus macaques exposed to potentially lethal doses of radiation includes the medical management consisting of intravenous fluids, prophylactic antibiotics, blood transfusions, anti-diarrheals, analgesics, and nutrition (Farese et al. 2012).

In addition to the TBI model, a special model using partial body irradiation sparing 5% of the bone marrow (PBI/BM5) during exposure was developed within the MCART consortium (Medical Countermeasures Against Radiological Threats) for analysis of long-term survival from the H-ARS or GI-ARS. This model is utilized to mimic a survivable, high-dose exposure in a nuclear terrorist and/or accident scenario (MacVittie et al. 2012).

In this NHP model medical management – including anti-diarrheals, analgesics, antibiotics, and even blood transfusion – is administered depending on clinical signs and symptoms. Therefore, the clinical course will be even more comparable with that of radiation accident victims treated in a hospital. This is one of the greatest advantages of this existing NHP model and the data from these NHP studies.

For the comparison of clinical data from radiation accident victims from the database SEARCH and data from the NHP model, two exposure regimes will be analysed. The TBI NHP model with 10 and 11.5 Gy exposure is regarded to be equivalent to the METREPOL H4 category of effect in the hematopoietic system. On the other hand, the PBI/BM5 NHP model seems to be an excellent model for the METREPOL H3 category, since the spared bone marrow permits autologous recovery of the hematopoietic system.

Objectives of the Project

The goal of the project is to evaluate and analyze the human radiation exposure data base SEARCH and compare that data base compiled and analyzed for the NHP experimental data relative to the TBI and PBI/BM5 models. This comparison will then contribute to the validation of the NHP model.

The Project contains the following objectives

Explore the structure and content of the NHP experimental data base—Prepare a consensus format for the NHP data base that enables efficient adaptation of the NHP data structure to the case history data structure of the SEARCH database.

Develop the basic matching criteria for patient selection—Since the general objective is to compare and correlate NHP and human clinical signs and symptoms along the time course after radiation exposure, suitable patients must be selected from the human case

history data base. We will define clear criteria and conditions to ensure the comparability and to prepare identification of SEARCH cases.

Identification of suitable patients—According to the criteria and conditions defined above, individual patients will be selected. Each patient will have to be reassessed using their complete set of clinical information.

Extraction and reformatting of data—Patient data extracted from SEARCH will have to be reformatted to some degree (e.g., reformatting of time-point to time-span after exposure and similar) to prepare clinical assessment.

Analysis and comparison of matched NHP and human data sets—This objective is the core of the project. It will determine the similarities and differences in the clinical time course of NHP and humans after acute radiation exposure to assess the validity of utilizing NHP experimental models to guide the medical treatment of human patients.

The matched NHP and human data sets will be analyzed according to similarities and differences using the respective post-exposure time course parameters for the following organ systems:

- Hematopoietic system (H-ARS)
- Gastrointestinal system (GI-ARS)
- Multi-organ involvement; lung and other

Preliminary Results

The structure and content of the NHP experimental data base was analysed and compared with the structure and content of the SEARCH database. To optimize compatibility between the NHP and human data, data were converted with respect to the findings of the first project objective, “Explore the structure and content of the NHP experimental data”.

The comparison of SEARCH cases and NHP data should include as many organ systems as possible, but should definitely cover the four major organ systems known to be affected by acute radiation exposure, as described in the METREPOL system (hematopoietic, skin, gastrointestinal, and neurovascular).

Therefore the following matching criteria for patient selection were defined:

- Complete data regarding the time course of effect in the hematopoietic system. The most important data are from differential blood counts.
- Identification of sufficient data to analyze the time course of effect in the gastrointestinal system.
- Identification of all data relevant to multi-organ-involvement and failure, to include as much clinical data as possible regarding the other important organ systems.

The SEARCH database was analyzed with regard to the basic matching criteria for patient selection. For suitable patients, METREPOL grading of the hematopoietic system had to be performed. From all identified cases we were able to identify a group of 10 patients with METREPOL grading H4 and a group of 20 patients with grading H2/H3 suitable for comparison with NHP data.

The SEARCH data were then extracted and reformatted for comparability with the NHP data. To compare the time course of the ARS, medical treatment also has to be analysed in

the SEARCH cases. Treatment modifies the kinetics of acute radiation effects, e.g., transfusion and administration of cytokines will modify the clinical course of radiation effects on the hematopoietic system and peripheral blood count analysis. Some SEARCH cases were administered hematopoietic stem cell transplants (HSCT), in some cases with uncertain sufficiency and indication.

Since NHP were treated with a standardized treatment regime including transfusions, we hypothesize the clinical course and alterations in the blood cell counts will be comparable with SEARCH cases treated in a hospital.

Available data about the cell counts from peripheral blood from the SEARCH database as well as from the NHP data were used to compare the time course of the hematopoietic syndrome. Neutrophil granulocytes are of main interest because of their kinetic and their pathophysiological consequences. We compared the data available in the SEARCH database termed “granulocytes” with the NHP data termed “absolute neutrophil count”.

In the SEARCH database, most of the patients graded METREPOL H4 did not survive the acute phase of the ARS, even if HSCT was performed. No patient in the selected group of 10 cases graded H4 survived the acute phase of the ARS. Survival time in the H4 cases ranged from 14 to 30 days (mean survival time = 19.2 days). This is very similar to the NHP TBI group with exposure to 10 and 11.5 Gy.

To compare the kinetic of neutrophil granulocytes the data of all 10 patients of the SEARCH H4 group (figure 1) and all 14 available individuals of the NHP TBI model (figure 2) are presented. The time course of the hematopoietic syndrome is in principle similar in the SEARCH H4 cases and the NHP TBI model (10 and 11.5 Gy), except for the more rapid decline of cell numbers in the NHP model.

To compare the kinetic of neutrophil granulocytes the data of all 20 patients of the SEARCH H2/H3 group (figure 3) and all 20 available individuals of the NHP PBI/BM5 group (figure 4) are presented. In the group of the 20 SEARCH cases graded H2 and H3, all patients survived the acute phase of the ARS. The time course of the hematopoietic syndrome appears to be comparable between the SEARCH H2/H3 and the NHP PBI/BM5 group, which again exhibited a more rapid decline in cell numbers, and an earlier onset of autologous recovery of the hematopoietic system.

The analysis of GI parameters is also based on 30 SEARCH patients (10 patients with category H4 and 20 patients with category H2/H3).

We observed the incidence of diarrhea according to the WHO definition in all 30 cases. Later we compared these clinical time courses to the occurrence of diarrhea-like stool consistency in 20 PBI/BM5 NHP.

In the H2/H3 cohort, 61.1% had diarrhea (WHO definition) during their hospital stay. 17% of the H2/H3 cohort suffered from diarrhea on day 0 (day of irradiation). That early onset (prodromal stage) was followed by an interval without any occurrence of diarrhea (latent stage). In the following clinical time course, the incidence of diarrhea increased slightly, reaching a peak (33% had diarrhea) at day 31 (stage of manifest illness).

The H4 patients showed a similar clinical time course, but the daily occurrences of diarrhea were higher. 44% of those patients had diarrhea at day 0, but the latent stage was shorter, and the peak incidence was reached on day 13.

The NHP had no occurrence of diarrhea in the prodromal stage (days 0 and 1), which was most likely due to fasting prior to irradiation. In the following time course, the percentage of animals with diarrhea grew strongly, reaching a maximum of 80 % at day 7.

The SEARCH patients of both cohorts suffered from vomiting during the first 2 days. The patients without vomiting during prodromal stage didn't vomit at all. The incidence and severity of vomiting in the NHP is considerably influenced by administration of Ondansetron both immediately pre- and post-irradiation.

Conclusion

The core objective of the project is the analysis and comparison of matched NHP and human data sets. It will determine the similarities and differences in the clinical time course of NHP and humans after acute radiation exposure to assess the validity of utilizing NHP model data in the medical treatment of human patients.

The SEARCH database was analyzed with regards to the basic matching criteria for patient selection, and we were able to identify a group of 10 patients with METREPOL grading H4, and a group of 20 patients with grading H2/H3 suitable for comparison with NHP data.

The SEARCH data were then converted and reformatted for comparability with NHP data.

A first comparative analysis of the data showed that, in principle, the time course of the ARS in the hematopoietic system and in the GI-tract is comparable between species. Now further analysis and case by case analysis will be performed to determine in detail how to compare the time courses and their modifications due to therapeutic measures within the identified data. Since treatment will modify the kinetics of acute radiation effects (e.g., transfusion and administration of cytokines will modify the clinical course of radiation effects on the hematopoietic system and peripheral blood count analysis), they have to be taken into account in the comparative analysis of the data. The analysis of multi-organ involvement will require extensive work and seems to be one of the most difficult parts of the project. Here, reasonable approaches which can be used across the species barrier have to be defined and tested for usability.

It is anticipated that this project will contribute to the validation and interpretation of the valuable data from the NHP studies.

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References

Dainiak N, Gent RN, Carr Z, Schneider R, Bader J, Buglova E, Chao N, Coleman CN, Ganser A, Gorin C, Hauer-Jensen M, Huff LA, Lillis-Hearne P, Maekawa K, Nemhauser J, Powles R, Schünemann H, Shapiro A, Stenke L, Valverde N, Weinstock D, White D, Albanese J, Meineke V. Literature review and global consensus on management of acute radiation syndrome affecting non-hematopoietic organ systems. *Disaster Med Public Health Prep.* 2011; 5:183–201. [PubMed: 21986999]

- Farese AM, Cohen MV, Katz BP, Smith CP, Jackson W 3rd, Cohen DM, MacVittie TJ. A nonhuman primate model of the hematopoietic acute radiation syndrome plus medical management. *Health Phys.* 2012; 103(4):367–82. [PubMed: 22929469]
- Flidner, TM.; Friesecke, I.; Beyrer, I., editors. *Medical Management of Radiation Accidents: Manual on the Acute Radiation Syndrome*. British Institute of Radiology; London: 2001.
- Flidner TM, Dörr HD, Meineke V. Multi-organ involvement as a pathogenetic principle of the radiation syndromes: A study involving 110 case histories documented in SEARCH and classified as the bases of hemopoietic indicators of effect. *Br J Radiol Supplement.* 2005; 27:1–8.
- Friesecke I, Beyrer K, Wedel R, Reimers K, Flidner TM. SEARCH: a system for evaluation and archiving of radiation accidents based on case histories. *Radiat Environ Biophys.* 2000; 39:213–7. [PubMed: 11095152]
- MacVittie TJ, Farese AM, Bennett A, Gelfond D, Shea-Donohue T, Tudor G, Booth C, McFarland E, Jackson W 3rd. The acute gastrointestinal subsyndrome of the acute radiation syndrome: a rhesus macaque model. *Health Phys.* 2012; 103(4):411–26. [PubMed: 22929470]
- MacVittie TJ, Bennett A, Booth C, Garofalo M, Tudor G, Ward A, Shea-Donohue T, Gelfond D, McFarland E, Jackson W 3rd, Lu W, Farese AM. The prolonged gastrointestinal syndrome in rhesus macaques: the relationship between gastrointestinal, hematopoietic, and delayed multi-organ sequelae following acute, potentially lethal, partial-body irradiation. *Health Phys.* 2012; 103(4): 427–53. [PubMed: 22929471]

Figure 1.
Granulocyte count [Giga/l] for all individuals of the SEARCH H4 group from the day of radiation exposure on.

Figure 2.
Absolute neutrophil count [Giga/l] for all TBI NHP 10 and 11.5 Gy irradiation.

Figure 3.
Granulocyte count [Giga/l] for all individuals of the SEARCH H2/H3 group from the day of radiation exposure up to 60 days.

Figure 4.
Absolute neutrophil count [Giga/l] for all PBI/BM5 NHP with 12 Gy, 11,5 Gy, 11 Gy, 10 Gy and 9 Gy irradiation.