Radiol Oncol 1997; 31: 309-14.

Diagnosis and treatment of radiation damage – the acute radiation syndrome

Susanne Klutmann, Karl H. Bohuslavizki, Winfried Brenner, Eberhard Henze

Department of Nuclear Medicine, Christian-Albrechts-University of Kiel, Germany

Radiation mainly yields to a damage of highly reproductive cells, i.e. radiosensitive tissues like bone marrow, gastrointestinal mucosa, and hair follicles. With increasing doses radiation causes damage of more differentiated, i.e. relatively radioresistant organs like the central nervous system as well. The acute radiation syndrome presents with an uniform sequence of 3 phases: the prodromal stage with unspecific symptoms like vomiting and nausea, followed by a phase of subjective well-being, i.e. the latency phase. The third phase of the acute radiation syndrome has been divided into three major catagories: 1. bone marrow syndrome, 2. gastrointestinal syndrome, and 3. central nervous syndrome. Each syndrome is defined by dose, survival time, and symptoms. Survival of the patients is mainly limited by radiogenic damage to the bone marrow, and causal treatment like bone marrow transplantation may be successful after whole-body irradiation below 10 Gy. Whereas after applied doses above 10 Gy the therapeutic approach will predominantly be palliative preventing patients from pain and suffering.

Key words: radiation injuries-diagnosis-therapy

Introduction

The development of radiation biology began immediatly after the discovery of the X-rays by Konrad Wilhelm Röntgen in 1895. Apart from the usefulness of radiation in medicine and technology radiation-induced damages were observed soon after the first applications of X-rays. Becquerel and Curie suffered from an acute radiation dermatite, the so called radium burn. Curie died of aplastic anemia probably due to chronic radiation exposure. Since the tragedy of Hiroshima and Nagasaki and the accident that occured at the Chernobyl nuclear power station in april 1986[1] the awareness of the hazards of radiation has been increased. Due to these tragedies human data on the effects of a single-body radiation could have been obtained.

Even if radiation syndromes are very rare cases in clinical routine patient management, the knowledge of both their clinical symptoms and treatment should be of interest not only for those professionals dealing with X-rays. However, the clinical symptoms depend on the body region exposed, and the level of the radiation dose as well as on the duration of radiation exposure. Therefore, clinical symptoms of radiation syndromes show a great variation. The symptoms occuring promptly include simple skin reactions as well as the acute radiation syndrome. On the other hand, the development of neoplasms are well-known as late side effects caused by radiation. Since data on humans being exposed to whole-body irradiation are well-known the sequence and intensity of clinical symptoms may be used to estimate the radiation dose to which an individual was exposed accidentally.

In this paper we describe both basic mechanisms and effects of radiation in different tissues as well

Correspondence to: Dr. Karl H. Bohuslavizki, Department of Nuclear Medicine, Christian-Albrechts-University of Kiel, Arnold-Heller-Str. 9, D-24105 Kiel, Germany
Tel.: +49 4 31 5 97 – 30 76, Fax.: +49 4 31 5 97 – 30 65

UDC: 616-001.26-07-08

as clinical symptoms of radiation injury. The latter is examplified by a radiation accident which happened in Israel in 1990.

Basic mechanisms of radiation damage

The interaction of radiation with tissue occurs within seconds. In the first physical stage high energetic particles deposit their energy within 10^{-18} to 10^{-12} seconds predominantly in water molecules. In the following physico-chemical stage activated particles transfer their energy to biological molecules, thereby producing free radicals via ionization. These radicals interact in the so called chemical stage with surrounding biological molecules, e.g. DNA, RNA or the core membrane. The altered biological molecules lead to delayed biological effects of radiation within hours, days or even years. Thus, it is reasonable that biological effects of radiation mainly depend on the amount of energy (Joule per kilogramm = Gy) absorbed in tissues.

Since different types of radiation yield to same physico-chemical effects, i.e. the ionization with consecutive production of free radicals, their biological effects are mainly comparable. However, different types of radiation differ in their amount of free radicals generated per unit of energy and, thus, different types of radiation produce varying degrees of damage with the same dose. This different relative biological effectiveness is due to the fact that the linear energy transfer (LET) for each type of radiation is different: For the same total dose, the radiation of high LET (alpha particles: LET = 20) produces greater damage than that of low LET radiation (X-ray and gamma-ray: LET = 1).

Molecular damage

Molecular damage caused by radiation is based on different mechanisms. From an absorbed dose of 1 mGy single-strand breaks of DNA occur in 50 % of the irradiated cells. However, both single-strand and double-strand breaks of DNA are repairable, thus changes in the genome are effectively avoided.[2-5] From 0.1 to 1 Gy the biosynthesis of DNA, RNA and proteins (in sequence of their decreased sensitivity) is reduced. The production of antibodies is altered from an absorbed dose of 2 Gy.

The radiosensitivity of different cytoplasmic organelles differs. The nucleus and its membrane are more radiosensitive than other subcellar structures such as mitochondria, lysosomes, cell membrane und the golgi apparatus. In addition, the radiosensitivity of the cell is related to the cell cycle which is divided into four phases. During the mitosis (M) period and the post-DNA synthesis phase (G2) the cell is more radiosensitive than in the late pre-DNA synthesis period (G1). On the other hand, cells are relativly radioresistant during the non-growth period (G0) and the DNA synthetis phase (S).

The technique of obtaining synchronized cells has improved new tumor therapies: prior to irradiation tumor cells are synchronized by cell toxines in order to increase their radiosensitivity.

Effects of radiation on organs

In 1906 Bergonié and Tribondéau formulated some references concerning the radiosensitivity of cells: X-rays are more effective on cells that have a greater reproductive actvity. X-rays are more effective on cells of which the morphology and the function are the least fixed.

Thus, highly radiosensitive tissues are those with a high reproductive potency, e.g. bone marrow, lymphatic tissues, reproductive organs, mucosa of the gastrointestinal tract and hair follicles. Conversely, less radiosensitive are skin, eyes, liver, lung, and kidneys. A relative radioresistance has been observed in several tissues, e.g. central nervous system, heart, muscles, bones and fat tissue.

Bone marrow syndrome and lymphatic syndrome

Undifferentiated stem cells of the bone marrow are highly radiosensitive cells. Directly after radiation exposure granulocytosis as initial reaction of the bone marrow can be observed. This is followed by a leucopenia within hours due to a depressed cell production of stem cells located in the bone marrow.

Radiation-induced bone marrow damage is influenced by dose rate: the higher the dose rate the greater the damage. An absorbed dose of 2.5 Gy destroys 5 % of the stem cells, whereas after a radiation exposure of 6.5 Gy only 5 % of the stem cells maintain their ability to proliferate. Therefore, a little increase of the absorbed radiation dose causes a marked increase in the number of destroyed stem cells. This illustrates the extreme steepness of the underlying dose-effect-curve.

The sequence of cell reduction in the peripheral blood is uniform. This mainly reflects the difference of mean life-time of the different cell types in the peripheral blood. After a whole-body irradiation of 5-10 Gy the number of lymphocytes decreases within hours and days followed by a reduction of granulocytes and thrombocytes. A decline of erythrocytes is seen from the third week after exposure according to their longer mean life-time.

Gastrointestinal tract

The signs and symptoms associated with the gastrointestinal syndrome may be due to the failure of both intestinal mucosa and the bone marrow.[6] Effects of radiation on the gastrointestinal tract are widely varying. An exposure of 4 Gy decreases the motility of the small intestin. After 10 Gy a decreased production of hydrochloric acid can be observed followed by fluid and electrolyte imbalance. This imbalance is due to a failure of intestinal absorption which leads to diarrhea and severe dehydration. The gastrointestinal damage is also associated with infection. Therefore, postirradiation infection may be due to the failure of the intestinal mucosa as well as to the failure of the irradiated bone marrow. The radiation-induced changes of mucosa membranes in association with the decreased motility may lead to the clinical picture of a radiogenic ileus as a late side effect of irradiation.

Skin

Skin changes following radiation of the respective anatomical region differ between individuals. Furthermore, different structures of the skin show a different radiosensitivity. Hair follicles are highly radiosensible. An absorbed dose of as less as 1 Gy leads to an inhibition of growing hair follicles. 4 Gy produce a temporary and 20 Gy a permanent epilation. From a radiation dose of 10 Gy an initial erythema may appear according to capillary dilatation and release of histamine-like substances: the acute radiation dermatite. Months after an irradiation epidermis becomes atrophic associated with variations of pigmentation, fibrosis and ulcerations due to rarified vascularization. As late side effect of radiation skin neoplasms such as spinalioma may occur.[7]

Eyes

Different radiosensitivity occurs in different structures of the eyes as well. The most radiosensitive part of the eye is the lens, whereas retinal tissue and the optic nerve are relatively radioresistent. After low radiation doses conjunctivitis, blepharitis and an epilation may occur. From a radiation dose of 10 Gy corneal ulcerations may appear as well as radiogenic cataracts.

Nervous system

Nerval tissue consisting of well differentiated cells with an absence of reproductive activity is markedly radioresistant. The spinal cord is the most radiosensitive substructure in the central nervous system.[8] Radiogenic damage of the spinal cord occurs from 40 Gy with consecutive neurological signs. Postirradiation effects have been observed such as post radiation myelitis, and hyaline thickening of blood vessels with the development of paralysis.[9, 10] In contrast, glial cells like astrocytes, schwann cells or oligodendrocytes have still reproductive activity and, therefore, they are much more radiosensitive.

Bone

The mature adult skeleton is well differentiated and for this reason relatively radioresistant. On the other hand, bones of the adolescents may easily be damaged by radiation causing a retardation of growth. In case of unilateral application of irradiation an asymmetric growth with inherent orthopedic problems can be observed.

Respiratory system

Although lung and pleura are relatively radioresistant clinical signs of lung fibrosis and pneumonia may occur after high dose irradiation. Moreover, irradiated lungs have a higher risk of secondary diseases, e.g. emphysema following chronic bronchitis, atelectases or neoplastic disorders.

Acute radiation syndrome

General considerations

The acute radiation syndrome has an uniform sequence of symptoms. The prodromal stage is characterized by headache, nausea and vomiting within 1 to 2 days. These symptoms subside as rapidly as they develop. Thereafter the patient feels more comfortable which is called the latency phase. From the third day after radiation exposure the main symptoms of the acute radiation syndrome may occur such as the bone marrow syndrome, the gastrointes-

tinal syndrome or the central nervous system syndrome. The intensity, the time course, and the number of symptoms depend on the radiation dose applied. With increasing radiation doses more symptoms appear earlier, and symptoms are more pronounced.

Prodromal stage

The prodromal stage is defined by symptoms occuring within the first 48 hours after radiation exposure. The cardinal symptom of the prodromal stage is vomiting with nausea and lack of appetite. The time of occurence of symptoms can be used as a prognostic factor *quoad vitam* to estimate the radiation dose applied accidentally. If vomiting occurs within two hours after radiation the dose will be potentially lethal. Vomiting within 30 minutes after irradiation is considered being a sign of a certain lethal dose.

Moreover, there may be some more uncharacteristic symptoms occuring in the prodromal stage, i.e. fever, erythema of the conjunctiva as well as erythema of the oropharyngeal mucosa. The latter points on a dose higher than the LD_{50}. The central nervous system may present with confusion, convulsion and unconsciousness in the prodromal stage.

The therapy of the prodromal stage is limited to palliative treatment, e.g. effective antiemetics.

Latency phase

The latency phase is characterized by subjective well-being for about 1-2 days. This is due to the relatively radioresistant differentiated cells which are still able to function until their physiological degradation. Thus, symptoms of acute radiation syndrome occur when there is a lack of supplies caused by the radiation-induced damage of highly reproductive stem cells.

Radiation syndromes after latency phase

The signs and symptoms produced by whole-body exposure are referred to as the radiation syndrome. Radiation syndromes have been divided into three major catagories: 1. bone marrow syndrome, 2. gastrointestinal syndrome, and 3. central nervous syndrome. Each syndrome is defined by dose, survival time, and symptoms.

Bone marrow syndrome

Bone marrow syndrome is defined by bone marrow depletion with subsequent pancytopenia yielding to a consecutive decrease of lymphocytes, leukocytes, and platelets within hours to days in the peripheral blood. This is followed by a delayed decrease of red blood cells within days to weeks. The pancytopenia following irradiation is the primary reason for death in bone marrow syndrome.

For the patient´s survival the vitality of a few stem cells in the bone marrow is required. Model calculations revealed that as less as 0.8 % surviving stem cells in the bone marrow are sufficient to maintain the patient´s survival. However, the dose-effect-curve is extremly steep. Consequently, only little differences in the dose applied cause marked changes of the survival rate. Thirty days after whole-body exposure with 2,5 Gy 95 % of patients are still alive whereas a dose of 6,5 Gy kills 95 % of patients. Thus, a 3 fold increased whole-body radiation dose decreases the patient's survival rate by the factor 20.

The clinical symptoms are mainly caused by the pancytopenia. Due to low platelet counts hemorrhagia may occur. A marked neutropenia increases the susceptablility to infection, i.e. infection with opportunistic germs. Concomitant damage of the gastrointestinal tract leads to fluid and electrolyte imbalance.

The therapy of bone marrow syndrome is adapted to the clinical symptoms. This includes application of antibiotics, antimycotics, infusion of platelets, and the balanced substitution of fluid and electrolytes. Moreover, cytokines may be helpful to accelerate differentiation of stem cells. Bone marrow transplantation may be considered in patients with whole-body doses of less than 10 Gy as the only causal therapeutic approach.[11-13]

Gastrointestinal syndrome

The gastrointestinal syndrome is characterized by a damage of mucosa. Complete destruction of proliferating basal cells in the upper gastrointestinal tract, e.g. duodenum and jejunum, can be observed from radiation doses of 10 Gy.

The clinical symptoms are directly derived from the damage described above. Patients may show up with diarrhea, mucosal ulcerations, malabsorption syndrome, fluid and electrolyte imbalance as well as with septic shock caused by an overgrowth of intestinal germs in these immunodeficient patients.[14]

The therapeutic approach is similar to that of treatment of bone marrow syndrome. This includes application of antibiotics, antimycotics, infusion of

platelets, and the balanced substitution of fluid and electrolytes as well as parenteral nutrition of the patients. Since gastrointestinal syndrome may occur even below whole-body doses of 10 Gy bone marrow transplantation may be considered useful in these patients.

Central nervous syndrome

The main pathogenetic mechanism of central nervous syndrome is a damage of small vessels. The resulting vasculitis leads to central edema via an increased permeability of capillaries. The central nervous syndrome is characterized by periods of agitation and apparent marked apathy, followed by signs of disorientation, disturbed equilibrium, ataxia, diarrhea, vomiting, opisthotonus, convulsions, prostration, coma and death. Death probably results either from a direct neuronal damage or via increased intracranial pressure.[15-18]

The therapeutic approach is directed against pain and convulsion, and vomiting in order to relief patients from suffering. Thus, this predominantly palliative treatment consists of analgetics, sedative agents, and antiemetic drugs.

Radiation accident in Soreq (Israel) on 21st of June 1990

On June 21st 1990 due to technological failure and human error a serious nuclear accident occured at the nutrition radiation factory in Soreq in Israel. A 32-years-old employe was irradiated by a highly active Co-60 source for the duration of about 2 minutes receiving a whole-body dose of some 20 Gy. Within 5 minutes after exposure he started vomiting. Consequently, he was submitted to the Tel Aviv hospital 2.5 hours after the accident. On admission he presented abdominal pain, nausea, persistant vomiting, generalized erythema, blepharoedema, and an increased body temperature of 40.7 °C. 8 hours after exposure he was transferred to the bone marrow transplantation unit in Jerusalem.

Due to suspected immunodeficiency the patient was isolated and his intestine was sterilized by oral antibiotics. To prevent viral infection the patient was treated with Aciclovir. The application of cytokines was performed in order to accelerate differentiation of vital stem cells due to massiv pancytopenia. Bone marrow transplantation was performed 4 days following irradiation. However, the donor, his brother was not perfectly compatible in his MHC-antigens. At the end of the first week the patient continued vomiting and exhibited both liquid and hemorrhagic diarrhea, i.e. gastrointestinal syndrome. Coloscopy revealed marked colitis with edema, hyperemia and multiple ulcerations. This was accompanied by oropharyngeal mucositis and an epilation of head, face, and pubic hair. Due to gastrointestinal syndrome the patient received parenteral alimentation in order to substitute the imbalance of fluid and electrolytes.

In the second week multiorgan failure occured with progressive decrease of renal and hepatic function. The patient developped abacterial pneumonia caused by cytomegaly virus, which was treated by virostatics. The patient became more and more disorientated on day 35 post irradiation, and died on the following day due to respiratory failure.

Conclusion

Although acute radiation syndrome is a rare problem in current clinical practice one should be aware of the signs and symptoms in order to ensure both immediate diagnosis and adequate subsequent treatment in case of radiation accidents.

References

1. Perry AR, Iglar AF. The accident at Chernobyl: radiation doses and effects. *Radiol Technol* 1990; **61**: 290.

2. Leontjeva GA., Manzighin YA, Gazier AL. The ultrafast repair of single strand breaks in DNA of gamma-irradiated chinese hamster cells. *Int J Radiat Biol* 1976; **30**: 577.

3. Cleaver JF. DNA repair and radiation sensitivity in human (xeroderma pigmentosum) cells. *Int J Radiat Biol* 1970; **18**: 557.

4. Brant TP, Wheatley GA. Repair and replication of X-irradiated HeLa cell DNA. *Int J Radiat Biol* 1971; **19**: 339.

5. Elkind MM, Sutton-Gilbert H, Moses WB, Kammper C. Sublethal and lethal radiation damage. *Nature (London)* 1967; **214**: 1088.

6. Quastler H, Lanzle EF, Keller ME, Osborne JW. Acute intestinal radiation death studies on roethen death mice. *Am J Physiol* 1951; **164**: 546.

7. Allen, KDA, Frred JH. Skin cancer: correlation of field size and cancerocidal dose in roentgen treatment. *Am J Roentgenol* 1956; **75**: 581.

8. Boden G. Radiation myelitis of the cevical spinal cord. *Br J Radiol* 1948; **21**: 464.

9. Wilson SG. Radiation-induced central nervous system death: a study of the pathological findings in monkeys irradiated with massiv doses of cobalt-60 (gamma) radiation. *J Neuropathol Exp Neurol* 1960; **19**: 195.

10. Clemente CD, Holst EA. Pathological changes in neurons, neuroglia and blood brain barrier induced by X-irradiation of heads of monkeys. *Arch Neurol Psychiatry* 1954; **71**: 66.

11. Mathe PF, Bernard J, Schwartzenberg L, Larrieu MF, LaLanne CM, Dutreix A, Deneux PF, Surmount J, Schwarzmann V, Ceora B. Attempts at treatment of leucemic subjects following remission by total body irradiation followed by transfusion of homologous marrow. *Rev Fr Etud Clin Biol* 1959; **4**: 625.

12. Beilby JOW, Cade IS, Jeliffe AM, Packin DM, Stewart JW. Prolonged survival of a bone marrow graft resulting in a blood-group chimera. *Br Med J* 1960; **1**: 96.

13. Thomas ED, Lochte HL Jr, Ferrebee JW. Irradiation of the entire body and marrow transplantation: some observations and comments. *Blood* 1959; **14**: 1.

14. Cronkite EP, Jacobs GC, Breecher G, Dillard GHL. The hemorrhagic phase of acute radiation injury. *Am J Roentgenol* 1952; **67**: 796.

15. Bond VP, Fliedner TM, Cronkite EP. Evaluation and managment of the heavily irradiated individual. *J Nucl Med* 1960; **1**: 221.

16. Kury G, Warrne S, Chute RN. Supralethal total body x-irradiation. *Arch Neurol* 1968; **18**: 703.

17. Gangloff H, Hug O. The effects of ionizing radiation on the nervous system. *Adv Biol Med Phys* 1965; **10**: 1.

18. Rider WD. Radiation damage to brain – a new syndrome. *J Can Assoc Radiol* 1963; **14**: 67.