INTRODUCTION

On the evening of November 8, 1895, W. C. RÖNTGEN found that, in a dark room, if the discharge tube is enclosed in a sealed, thick black carton to exclude all light, a paper plate covered on one side with barium platinocyanide placed in the path of the rays became fluorescent even when it was as far as two meters from the discharge tube. Since the nature of these rays was then unknown, he gave them the name X-rays. This is the discovery of radiation.1) He received countless honorary doctorates and prizes, including the first Nobel Prize for Physics in 1901 for his discovery of the "remarkable rays".2) In the following year, acute skin disorders, eye pain, hair loss without dermatitis, and burns were reported. In a sense, this was also the beginning of radiation biology. In fact, a few years later, the first successful treatment of human skin cancer by radiotherapy was performed by two Swedish physicians.3)

In 1898, Marie CURIE and her husband Pierre CURIE discovered a new element “Radium” from the uranium ore that had 2.5 million times stronger exposure action to the photographic plate compared to Uranium. They received the Nobel Prize for Physics in 1903 for their discovery of the “Radium”.4) On 4th July 1934, Marie CURIE died at the age of 66 years from aplastic anemia that is believed to have been contracted from her long-term exposure to radiation.5) The damaging effects of ionizing radiation were not known at the time of her work, which had been carried out without the safety measures later developed. She had carried test tubes containing radioactive isotopes in her pocket and stored them in her desk drawer, remarking on the faint light that the substances gave off in the dark. She was also exposed to X-rays from unshielded equipment while serving as a radiologist in field hospitals during the war. Although the many decades of exposure to radiation caused chronic illnesses (including near blindness due to cataracts) and ultimately her death, she never really acknowledged the health risks of radiation exposure.

Radiation injuries depend on the individual, timing, degree of influence. Exposure doses can be classified as having stochastic effects and deterministic effects. Furthermore, affected individuals can be classified as having somatic effects and hereditary effects. Somatic effects depend on the length of the latency period and are classified as acute (early) and late injury.

Acute injury: These effects appear within weeks after exposure. On receiving a large amount of radiation in a relatively short period of time on a wide range of body or whole body, acute injuries occurred two to three months after exposure. Typically, the relationship between radiation exposure and acute injuries is clear. Acute injury is caused by cell death in tissues and organs.6) The exposure to a lethal dose of ionizing radiation can result in severe acute radiation syndromes (ARS) involving bone marrow death and gastrointestinal death. ARS causes a decrease in the peripheral blood cell count and gastrointestinal dysfunction, finally...
leading to death caused by immune deficiency. Half of the individuals exposed to 3–5 Gy of total body irradiation die from bone marrow death within 60 days.

Late injury: Late radiation injuries are typically observed after a latency period of 6 months or longer, and may develop many years after radiation exposure. These include radiation-induced carcinogenesis, genetic issues in offspring, and late organ effects such as thyroid dysfunction, cataracts, and infertility. It is distinct from ARS as it occurs at dose rates low enough to permit natural repair mechanisms to compete with the radiation damage during the exposure period.

In this manuscript, the overview of radiation-protective and mitigative agent development against acute radiation effects (external exposure) and the prospects for the future research are outlined.

II WHAT IS A RADIATION-PROTECTIVE AND MITIGATIVE AGENT?

Appropriate medical treatments should be performed immediately after radiation exposure. Although bone marrow transplantation (BMT) is available for recovery from radiation-induced bone marrow damage, BMT for victims in radiation accidents has many limitations, including histocompatibility, age constraints, HLA type and the fact that immunosuppression would be required to reduce the risk of graft versus host rejection. In contrast, pharmacological approaches can accommodate a large number of victims with few limitations. In the case of mass casualty incidents induced by radiation or radioactive compounds, the intake of appropriate medications is the most suitable initial treatment.

Generally, the radioprotector has been classified into four groups based on the mechanism of action as follows: radical scavenger, activators for the biophylactic mechanism, drug for systemic absorption and deposition prevention, and excretion promotion of radionuclide.

SINGH et al. and STONE et al. reported in their manuscript that medical countermeasures for radiation exposure are roughly divided into the following three classes. First, radioprotectors or radiation-protective agents are prophylactic agents that are administered before exposure to prevent radiation-induced cellular and molecular damage. Second, radiation mitigators are drugs administered shortly after irradiation that accelerate recovery or repair of radiation injury. Third, radionuclide eliminators are drugs that disrupt or block absorption of internalized radionuclides. Because this classification cannot be strictly distinguished, it is uniformly described as “radioprotectors” in this review.

Prussian blue has been approved as an internal marker according to the above classification. Prussian blue [ferric hexacyanoferrate (II)], which got its name from its use as a dye for Prussian military uniforms, was first produced as a blue dye in 1704 and has been used by artists and manufacturers ever since. Prussian blue dye and paint are still available today in art supply stores. This oral ion-exchange drug is indicated for decorporation of cesium and thallium and has been shown to be highly effective for 137Cs contamination.

In “Guidance levels for treatment with Prussian Blue”, at the lower guidance level (30 mSv), the radiation health benefit to the patient would be small, but for some patients, the discomfort and disruption of the treatment might be far outweighed by the reassurance provided and hence, it should be considered for treatment. At the upper guidance level (300 mSv), the overall benefit to the patient would be expected to be significant. Only in exceptional circumstances (be advanced age), a patient is not treated with a projected dose at this level. The Prussian blue treatment is best started within about seven days of intake but will still deliver a useful dose saving if the treatment commences within 28 days. Any radiation exposure should be reduced to as low as reasonably achievable, and so the treatment should continue until it no longer provides a significant reduction in committed effective dose. Usually, this indicates treatment duration of three to six months. A reduction in doses to 40–55% of those expected in the absence of treatment may be achievable.

SINGH et al. pointed out that radiation therapeutics or treatments are agents given when symptoms appear to stimulate repair or regeneration. Numerous candidate for radiation countermeasures (specifically radioprotectants and radiomitigators) have been identified and have been or are currently being developed for the U.S. Food and Drug Administration (FDA) approval.

III HISTORY OF EARLY TYPES OF RADIATION-PROTECTIVE AND RADIATION-MITIGATIVE AGENTS

In 1948, Patt discovered that cysteine could protect mice from the effects of total-body X-radiation if the drug was injected or ingested in large amounts before the radiation exposure. At about the same time, Bacq and his colleagues in Europe independently discovered that cysteamine could also protect animals from total-body irradiation. This compound has a structure represented by SH-CH$_2$-CH$_2$-NH$_2$. Although cysteine is a radioprotector, it is also toxic and induces nausea and vomiting at the dose levels required for radioprotection. A development program was initiated in 1959 by the United States Army in studies conducted at the Walter Reed Institute (Washington, DC) of Research with an aim to identify and synthesize drugs that can confer protection to individuals in a radiation environment without the debilitating toxicity of cysteine or cysteamine.

Over 4,000 compounds were synthesized and tested. It was discovered that the toxicity of the compound could be greatly reduced if the sulphydril group was covered by a phosphate group. Finally, WR-2721, S-[3-aminopropylamino]-ethylphosphorothioic acid (now known as amifostine) was found to be the most effective of those synthesized compounds. This is a phosphorylated aminothiol that has the potential to selectively protect normal tissues from damage by oxidative stress associated with cancer chemotherapy and radiotherapy.

At present, amifostine is the only radioprotective drug approved by FDA for head and neck cancer. It was originally developed as a clinically usable radioprotective agent from more than 4,000 compounds by the US Army Walter Reed Institute. Amifostine is a prodrug that is dephosphorylated
by the action of the membrane-bound alkaline phosphatase to the active metabolite WR-1065, 2-(3-aminopropyl)aminoethanol.\textsuperscript{[6, 26]} Radiation affects water molecules in tissues and cells and induces various types of free radicals that are highly reactive and interact rapidly with other cellular molecules (e.g., DNA, cellular membranes, and organelles). This metabolite is believed to be responsible for reducing the toxic effects of radiation in normal oral tissues and reducing the cumulative renal toxicity of cisplatin.\textsuperscript{[21, 22]} Probably due to free radical scavenging or chemical repair of damaged DNA. Many other studies regarding the radioprotective function have also been reported.

\textbf{Mori et al.} demonstrated the radioprotective effects of carbon particles treatment due to the reticuloendothelial system and the enhancement of hematopoietic recovery.\textsuperscript{[22–27]}

\section*{IV RADIATION-PROTECTIVE AND -MITIGATIVE ACTIVITIES OBSERVED IN NATURAL PRODUCT}

A number of materials that exhibit a radiation protective effect have been found in natural products. Some of them are shown below.

\textbf{Duan et al.} investigated procyanidins extracted with acetone-water from lotus (Nelumbo nucifera Gaertn.) seedpod (LSPCs) for in vivo radioprotective activity against whole body gamma irradiation in Swiss albino mice.\textsuperscript{[29]} Pretreatment with LSPCs 200 mg/kg by intragastric for 15 days was found to be the most effective dose in preventing radiation sickness, reducing radiation-induced mortality, increasing mean survival time, and elevating radiation median lethal dose from 8.9 to 10.5 Gy, indicating a dose modifying factor of 1.18. They concluded that LSPCs possess a strong whole body radioprotective activity, and it may be used as a radioprotector.

\textbf{Kim et al.} investigated the effects of extracts prepared from the red seaweed \textit{Callophylis japonica} on mice that were exposed to a sub-lethal dose of gamma radiation. Each fraction (100 mg/kg body weight) was administered intraperitoneally 2 times into the BALB/c mice, once at 1 h and once at 24 h before exposure to 9 Gy of \(\gamma\)-irradiation, showing that \(> 80\%\) of the mice remained alive at day 30.\textsuperscript{[29]}

\textbf{Kang et al.} investigated the radioprotective effect of phloroglucinol (1, 3, 5-trihydroxybenzene), a phlorotannin compound isolated from Ecklonia cava, against \(\gamma\)-ray radiation-induced oxidative damage \textit{in vitro} and \textit{in vivo}.\textsuperscript{[30]} Of the mice exposed to 7 Gy, 70% of the mice died by day 30 postirradiation. The mortality of irradiated mice pretreated with 100 mg phloroglucinol/kg body weight was significantly reduced at 30 days post-irradiation as compared to those of the other groups, showing 90% of the mice remained alive at day 30.

\textbf{Anzai et al.} have reported that mineral-yeast, especially Zn-yeast, provides remarkable post-irradiation protection against lethal whole body X-irradiation.\textsuperscript{[31]} The activity is mainly attributable to the insoluble fraction, whereas some soluble components might contribute to the additional protective activity.\textbf{Nishimura et al.} have investigated the influence of a host defense protein, lactoferrin (LF), contained in exocrine secretions such as milk on radiation disorder.\textsuperscript{[32]} They showed that the survival rate in LF-treated mice 30 d after irradiation was 92%, which is significantly higher compared to mice treated with saline (50%) (\(p = 0.0012\)). In addition, the LF showed hydroxyl radical scavenger activity \textit{in vitro}.

Cruciferous vegetables, such as cabbage, broccoli, and cauliflower, belong to the family Brassicaceae and are widely cultivated for food. These vegetables contain dietary supplementation with indole-3-carbinol (I3C), a phytochemical, which prevents tumors in animals.\textsuperscript{[33–38]} I3C is hydrolyzed to various products in the stomach, including 3,3-diindolylmethane (DIM), which is acid stable and a major bioactive metabolite.\textbf{Fan et al.} have reported that DIM is a potent radioprotector and mitigator that functions by stimulating ATM-driven responses to DNA damage-like response and NF-\(\kappa\)B survival signaling. DIM improved survival over a wide range of doses (5–13 Gy), suggesting that it can mitigate both gastrointestinal and hematopoietic injury.\textsuperscript{[39]}

\textbf{Liu et al.} have investigated that an orally administered hot-water extract from a Chinese herbal medicine, \textit{Cordyceps sinensis} (CS), protects mice from bone marrow and intestinal injuries after total-body irradiation (TBI).\textsuperscript{[39]} CS increased the median time to death from 13 to 20 days after 8 Gy TBI and from 9 to 18 days after 10 Gy TBI.

\textbf{Singh et al.} have investigated the aqueous extract of fruit pulp of Emblica officinalis (EO), an important drug used in Indian systems of medicine for several diseases, for its radioprotective properties against sublethal gamma radiation (9 Gy) in Swiss albino mice.\textsuperscript{[39]} The animals were fed with the extract for 7 consecutive days before irradiation. As a result, 100 mg/kg administration led to 87.5% survival at day 30. The components contained in EO significantly increased the concentration of the antioxidant enzymes and reduced lipid peroxidation, resulting in the increase in antistress activity.

\section*{V CYTOKINE AND ITS CLINICAL APPLICATION IN THE ACCIDENTS}

With the discovery of the gene recombination technology, many cytokines have been studied for their application in various medical fields such as neutropenia and renal anemia. Cytokines comprise numerous hormone-like, low-molecular-weight proteins that are secreted by various cell types to regulate the intensity and duration of immune responses and mediate cell-to-cell communication. Most cytokines are small (molecular weight: < 30 kDa) soluble proteins or glycoproteins produced by macrophages, B and T lymphocytes, mast cells, endothelial cells, fibroblasts, and stromal cells of the spleen, thymus, and bone marrow. Cytokines bind to specific receptors on the membrane of target cells, triggering signal-transduction pathways that ultimately alter the gene expression in the target cells and express the activity even in a small amount of pico mole level. Cytokines exhibit pleiotropy, redundancy, synergy, antagonism, and cascade induction, which permit them to regulate cellular activity in a coordinated, interactive way. A given cytokine that has different biological effects on different target cells has a pleiotropic action. Two or more cytokines that mediate similar functions are said to be redundant; redundancy makes it difficult to ascribe a particular
activity to a single cytokine. Cytokine synergism occurs when the combined effect of two cytokines on cellular activity is greater than the additive effects of the individual cytokines. In some cases, cytokines exhibit antagonism, i.e., the effects of one cytokine inhibit or offset the effects of another cytokine. Cascade induction occurs when the action of one cytokine on a target cell induces that cell to produce one or more other cytokines, which in turn may induce other target cells to produce other cytokines. Cytokine generates a complex network and regulates the production of other cytokines. Among them, one of the clinically useful and radioprotective important cytokine is granulocyte colony-stimulating factor (G-CSF). G-CSF is a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream.

G-CSF is a lineage-specific colony-stimulating factor produced by monocytes, fibroblasts, and endothelial cells. G-CSF also stimulates the survival, proliferation, differentiation, and function of neutrophil precursors and mature neutrophils. Currently, there are four recombinant G-CSF as approved pharmaceutical drugs in Japan: GranR (filgrastim, a G-CSF analog, Kyowa Hakko Kirin, Co., Ltd.), Neutrogen (lenograstim, Chugai Pharmaceutical Co., Ltd.), Neu-up (nartogristim, Yakult Pharmaceutical Industry Co., Ltd.) and G-lasta (polyethylene glycol-bound filgrastim, pegfilgrastim, Kyowa Hakko Kirin, Co., Ltd.). In our previous study, we investigated the effects of these three different types of recombinant human (rh) G-CSFs, Filgrastim, Nartogristim, and Lenograstim, on human granulocyte progenitor cells and expansion of neutrophils from nonirradiated or X-irradiated human CD34+ hematopoietic progenitor cells. We had demonstrated that the types of rhG-CSFs produced different effects when rhG-CSF was applied to nonirradiated CD34+ cells but not to X-irradiated CD34+ cells. However, we have to pay attention to the low levels of G-CSF after administration in vivo.

As described above, cytokines are characteristically synergistic. Many studies have made use of this feature. HERBOMIN et al. investigated early treatments with combinations of cytokines on the survival of B6D2F1 mice after 9 Gy of 60Co γ-irradiation. Then, stem cell factor (SCF), fms-related tyrosin kinase 3 ligand, thrombopoietin (TPO), interleukin-3 and keratinocyte growth factor were given at 2 hours and 24 hours post-total body irradiation (TBI). Erythropoietin (EPO) and Peg-filgrastim were given at 2 hours and 8 days post-TBI. Survival was monitored, and bone marrow hematopoiesis was evaluated at 300 days following early treatments. A combination of all cytokines administered early (2 hours and 24 hours) after lethal TBI induced 60% survival versus 5% in controls. In contrast, no effectiveness was observed, over antimicrobial supportive care, when administration of various combinations was delayed at 48 hours.

On September 30, 1999, the Tokai-mura criticality accident occurred at a nuclear fuel-processing facility run by JCO, an affiliate of Sumitomo Metal Mining, in Tokai-mura (70 miles northeast of Tokyo) as a result of an attempted shortcut in the protocol for processing nuclear fuel. In this accident, three workers were exposed to the neutron and γ-ray. Against bone-marrow suppression, hematopoietic factors, including G-CSF, granulocyte/macrophage-colony-stimulating factor (GM-CSF), TPO, and EPO were administered after peripheral blood stem-cell transplantation to the patients. At that time, TPO was not approved as a pharmaceutical drug as it was necessary to increase the number of platelets.

On March 11, 2006, a 50-year-old Caucasian male worker in a 60Co γ-radiation sterilization facility (specific activity, 800,000 Ci; dose rate 5 kGy/h) was exposed to the cobalt-60 sources (total activity 3 × 10^4 TBq) for 20 seconds, with an estimated total body irradiation of 4.2 Gy (3.8–5 Gy). On day 20 (March 31, 2006), the patient was admitted to the Percy Hospital (Clamart, France). Then, platelet injections began the next day, followed by cytokine injections [a combination of pegG-CSF, SCF and EPO] a week later (day 28). This multicytokine therapy accelerated the recovery of hematological reconstitution and achieved the blood parameters to normal ranges within 10 days, demonstrating the effectiveness in the bone marrow failure caused by radiation exposure.

The International Atomic Energy Agency recommends the principal therapeutic measures corresponding to different degrees of ARS severity (Table 1). Patients exposed to radiation doses exceeding 1 Gy should be observed. However, the use of cytokines shown in Table 1 depends on the country, and at least GM-CSF and IL-3 are not approved as pharmaceutical drugs in Japan.

VI DEVELOPMENT OF RECENT RADIATION-PROTECTIVE AND RADIATION-MITIGATIVE AGENTS

The development of radiation-protective and mitigative agents has been carried out mainly in Western countries. In the USA, the Armed Forces Radiobiology Research Institute (AFRRI) is a major research institute for drug development. This institute has provided many reports on drug development. SINGH et al. summarized their past and current efforts as follows: only three agents, OrbeShield, Ex-RAD, and BIO 300, demonstrated oral efficacy for ARS. Several agents have shown potential as radiomitigators that can be useful in a mass casualty scenario. CBBL502, HemaMax, AEOL 10150, and 5-AED have been evaluated in nonhuman primates and have shown encouraging results, and all these agents have been claimed as radiomitigators. CBBL502 and 5-AED also have efficacy as radioprotectors. The radioprotective efficacy of γ-tocotrienol (GT3), one of the eight distinct analogs of vitamin E, is currently being evaluated in nonhuman primates, and the initial indication is encouraging. A brief overview of each of the compounds is given below.

OrbeShield

OrbeShield contains BDP (beclomethasone 17, 21-dipropionate), which is a highly potent and topically active corticosteroid. In AFRRI’s website, the compound has been introduced as follows: the pre-clinical results indicate that dogs treated with OrbeShield demonstrated statistically significant (p = 0.04) improvement in survival with dosing at either 2 hours or 24 hours after exposure to lethal doses of total body irradiation (TBI) when compared to...
control dogs. OrbeShield™ appears to significantly mitigate the damage to the gastrointestinal epithelium caused by exposure to high doses of radiation using a well-established canine model of gastrointestinal ARS. It has been awarded the Orphan Drug and Fast Track Designations by the FDA for prevention of death following a potentially lethal dose of total body irradiation during or after a radiation disaster.49)

**Ex-RAD**

Ex-Rad is a small molecule kinase inhibitor developed for modifying cell cycle distribution patterns in cancer cells subjected to radiation therapy. It has also been identified as a potential candidate for radiation protection studies. GhiOSHI et al. have investigated its radioprotective efficacy using mice and in vitro models.60, 51) Thirty-day survival studies with C3H/HeN male mice revealed 88% survival when 500 mg/kg of Ex-Rad was injected subcutaneously 24 h and 15 min before irradiation with 8 Gy. They suggested that Ex-Rad’s radioprotective mechanisms involve the prevention of p53-dependent and independent radiation-induced apoptosis.

**BIO300**

LANDAUER et al. have investigated the radioprotective and behavioral effects of an acute administration of the isoflavone genistein (4', 5, 7-trihydroxyflavone) using mice and in vitro models.50, 51) The mice were administered a single subcutaneous (s. c.) dose of genistein either 24 h or 1 h before a lethal dose of gamma radiation (9.5 Gy of cobalt-60 at 0.6 Gy min⁻¹). They demonstrated that a single s. c. administration of the flavonoid genistein at non-toxic doses, 25 to 400 mg kg⁻¹, revealed 60 to 88% survival in irradiated mice.53)

**CBLB502**

CBLB502 is a polypeptide drug derived from Salmonella flagellin that binds to Toll-like receptor 5 (TLR5) and activates nuclear factor-κB signaling. BURDELYA et al. have demonstrated that a single injection of CBLB502 before the lethal total-body irradiation protected mice from both gastrointestinal and hematopoietic acute radiation syndromes and resulted in improved survival rates.54) They also demonstrated that CBLB502 injected after irradiation enhanced survival but at lower radiation doses. The United States FDA has granted investigational new drug status to CBLB502 as a radiation countermeasure for ARS, and it is currently under clinical development.9, 55)

**HemaMax / rh interleukin-12**

BASILE et al. mentioned that HemaMax, a rh interleukin-12 (rhIL-12), is under development to address an unmet medical need for effective treatments for acute radiation syndrome due to radiological terrorism or accident when administered at least 24 hours after radiation exposure.56) They have reported that this survival benefit was accompanied by increases of various kinds of cytokines in plasma. Furthermore, GLUZMAN-POLTORAK et al. have compared rhIL-12; 175 ng/kg × 1) with vehicle, granulocyte-colony-stimulating factor (G-CSF; 10 mg/kg/day × 18), or rhIL-12 + G-CSF after lethal irradiation in rhesus monkeys in a randomized, blinded, placebo-controlled study.57) They have shown that rhIL-12 alone increased erythroid, myeloid, and megakaryocyte counts relative to vehicle or G-CSF, indicating that a single injection of rhIL-12 significantly improved survival and promoted multilineage hematopoietic recovery in a nonhuman primate model of HSARS.

**AEOL 10150**

AEOL-10150 is currently being developed by Aeolus Pharmaceuticals, Inc. (Mission Viejo, CA) as a lead compound for the pulmonary effects of ARS. It is also the subject of

### Table 1 Principal therapeutic measures for acute radiation syndrome according to degree of severity.48)

| Whole body dose (Gy) | 1–2 | 2–4 | 4–6 | 6–8 | > 8 |
|---------------------|-----|-----|-----|-----|-----|
| Degree of severity of ARS | Mild | Moderate | Severe | Very severe | Lethal |
| Medical management and treatment | Outpatient observation for maximum of one month | Hospitalization | Isolation, as early as possible | G-CSF or GM-CSF as early as possible (or within the first week) | IL-3 and GM-CSF |
| | | | Antibiotics of broad spectrum activity (from the end of the latent period) | Antifungal and antiviral preparations (when necessary) | |
| | | | Blood components transfusion: platelets, erythrocytes (when necessary) | Complete parenteral nutrition (first week) | |
| | | | Metabolism correction, detoxication (when necessary) | Prophylaxis of disseminated intravascular coagulation (second week) | |
| | | | HLA-identical allogene BMT (first week) | Symptomatic therapy only | |

Note: BMT, bone marrow transplantation; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte macrophage-colony stimulating factor; IL-3, interleukin.
multiple U. S. Government-funded programs the aimed at developing the compound as a medical countermeasure against national security threats. AEOL 10150 has performed well in animal safety studies, is well-tolerated in two human clinical trials, and demonstrated efficacy in two species in ARS studies. RAHMANI et al. have determined whether the administration of a catalytic antioxidant, Mn(III) tetraakis(N, N-diethylimidazolium-2-yl) porphyrin, AEOL10150, reduces the severity of a long-term lung injury induced by fractionated radiation (RT). Fischer 344 rats received five 8 Gy fractions of RT to the right hemithorax. AEOL10150 was administered 15 min before RT and 8 h later during the period of RT treatment (5 days), followed by subcutaneous injections for 30 days, twice daily. They demonstrated that the administration of AEOL10150 at 5 mg/kg BID during and after RT results in a significant protective effect from long-term RT-induced lung injury.59)

5-AED / 5-androstenediol

SINGH et al. stated that 5-AED has been advanced as a possible countermeasure for treating the hematological component of ARS. WHITNALL et al. have investigated that a single subcutaneous injection of 5-AED 24 to 48 h prior to or 2 h after a lethal dose of TBI enhanced survival in mice. Although an injection 2 h after irradiation had lower efficacy than a pre-irradiation injection (i.e., 12% vs. 78%, respectively). They have investigated in vivo radioprotective efficacy of eleven steroids, 5-AED, 17α-androstenediol, dehydroepiandrosterone, 5-androstenediol, testosterone, estradiol, fluasterone, 16α-bromoeipandrosterone, 16α-fluoro-androst-5-en-17α-ol (α-fluorohydrin), and 16α-fluoro-androst-5-en-17β-ol (β-fluorohydrin) against mice 9–12.5 Gy for survival studies. From various experiments, they showed that the injection of mice with 80 mg/kg 5-AED one subcutaneous 24 hr before whole-body gamma-irradiation (11 Gy) resulted in complete survival. Later, the radioprotective efficacy of 5-AED was confirmed in studies conducted on irradiated mice and nonhuman primates (NHPs).61, 62)

Vitamine E analog

There are eight distinct analogs of vitamin E, designated α-, β-, γ-, and δ-tocopherol and α-, β-, γ-, and δ-tocotrienol. In particular, γ- and δ-tocotrienol have attracted attention as a single subcutaneous injection of 5-AED 24 to 48 h prior to or 2 h after a lethal dose of TBI enhanced survival in mice. However, a less toxic compound capable of suppressing both pathways should be prepared as a therapeutic inhibitor of p53. In addition, Atkinson and co-workers designed and produced oleic and stearic acid derivatives that targeted mitochondria and inhibit pro-apoptotic oxidative events, which led to cell death. By administering these derivatives to mice, they observed that radioprotective effects could be seen in mice treated 1 hour prior to 24 hours after irradiation. The authors suggested that the new ‘pro-oxidant’ enzymatic activity of certain protein complexes shown in this work represents a potential target for anti-apoptotic radioprotective drugs.

Recently, research related to novel radioprotective compounds has become increasingly focused on innate immunity; these compounds include agonists to various toll-like receptors (TLR), such as TLR-2, -3, -4, -5 and -6. The mechanism of action of some of the compounds have also been elucidated. However, the precise mechanism of action of radiation injury remain unclear for most effective compounds that have been reported to date. This is very important concern with regard to radioprotective drug development, particularly when combined with precise radiation dose evaluation/ biodosimetry. Moreover, some compounds may also induce adverse effects, such as enhanced inflammation in damaged tissues after exposure to radiation or increased proliferation of cancer cells.

VII RESEARCH EFFORTS AT HIROS AKI UNIVERSITY

We have also performed research on the development of radiation-mitigative agents in in vitro and in vivo studies. We have investigated the effects of epigallocatechin-3-gallate (ECGc), a major green tea polyphenol, on the growth of non-irradiated and X-irradiated CD34+ colony-forming unit-megakaryocyte which is prepared from human placental and umbilical cord blood and stimulated with a rhTPO in both semisolid and liquid cultures. EGCg has been widely
recognized as a powerful antioxidant and free radical scavenger, leading to investigations of its biological effects, which include radioprotective functions. Compared with previous studies, a relatively low concentration of EGCg (10–100 nM) yielded radioprotective effects against radiation damage in human megakaryocytopenia.79 Radiation exposure from a nuclear accident or a radiological attack may cause death from severe ARS, which results from radiation injury to key organ systems such as the hematopoietic and gastrointestinal system. Therefore, the top priority is to achieve reconstitution and restoration of hematopoiesis. BMT has previously been used to recover hematopoiesis in victims of radiological accidents, although it presents many challenges to a prompt response. In scenarios with many patients such as radiation accidents, the intake of appropriate medications is the most suitable initial treatment, and therefore, a stable supply and regular stockpile of approved pharmaceutical drugs are desired. In order to establish an optimum therapeutic protocol using the currently approved pharmaceutical drugs to increase the survival of victims exposed to lethal radiation, different combinations of four drugs—rhEPO, G-CSF, proto-oncogene myeloproliferative leukemia (c-mpl) receptor agonist romiplostim (RP) and nandrolone decanoate—were administered to mice within 2 h of exposure to a lethal 7 Gy dose of γ-irradiation.80 The radiomitigative activities of the eight combinations were estimated by the survival rates and hematological parameters, including the numbers of immature and mature blood cells, 30 days after γ-irradiation. The survival rate of the irradiated control mice gradually decreased, and all individuals died by day 27. In contrast, the combined administration of G-CSF, EPO and RP for five days immediately after irradiation led to a complete survival of the irradiated mice until day 30 (data not shown). The present findings show the possibility that a combination of three pharmaceutical drugs may be useful as a countermeasure for victims exposed to accidental lethal irradiation. We also found that RP alone led to a complete survival of the irradiated mice until day 30 (Fig. 1).77 The c-mpl ligand TPO and c-mpl receptor agonist act as radioprotective agents.78–80 One human c-mpl receptor agonist, RP, was recently approved for idiopathic thrombocytopenic purpura in several countries, including Japan. Stickney et al. reported that the duration of severe thrombocytopenia appeared to correlate with death to a greater extent than the duration of severe neutropenia.81 Thrombocytopenia appears to be more clinically relevant to survival in ARS than has been previously recognized. A recent study reported that the activation of TPO signaling by DNA damage activated the DNA repair function in hematopoietic stem and progenitor cells.82 However, the mechanism(s) involved in the increased survival would be needed in more detail.

VIII  CHALLENGES FOR THE FUTURE

The risk of radiation exposure due to radiological terrorism and radiological accidents caused by nuclear industry-related facilities that cause mass-casualty scenarios is increasing worldwide. In March 2011, a serious radiological accident occurred at the Fukushima-Daiichi nuclear power plant in Japan following the earthquake and tsunami.83 This accident shocked the world and is still affecting the Japanese society. Highly effective and completely safe medical countermeasures are needed, in addition to providing better ways to prevent and control radiological accidents in the future. Thus, a variety of issues still need to be addressed, such as the safety and efficacy of applications in humans, the optimal doses of the drugs, the optimal duration and timing of administration, and the applicable range of radiation doses that can be effectively countered. Studies to elucidate this information will be essential to establish a new medical countermeasure for accidental radiation exposure, and such studies will need to account for the medical circumstances of each country.

Kamran et al. pointed out, novel radioprotective agents, particularly for clinical radiotherapy, should be developed in such a way that they specifically target normal cells without conferring protection to tumor cells.84 The increased understanding of drug interaction with biological signaling and metabolic networks will be needed if we intend to improve the therapeutic index of novel radioprotective agents. Even if the acute radiation injury is avoided by these drugs, drugs should be developed such that they can also avoid long-term adverse effects such as carcinogenic and leukemia.

As a conclusion, in view of the progress of the previous studies on radiation protection agent, the following issues need to be solved in the near future.

1. Low molecular weight compound with a low toxicity
2. Effectiveness in the administration of post-irradiation
3. Preclinical evaluation in large animal models
4. No risk for carcinogenesis in the future after medications
5. Application to non-radiation medicine
6. Countermeasures against low-dose and long-term
radiation
In addition, the precise dose estimation in each exposed individual is also critical for the effective radiation emergency medicine. More precise experimental approaches are required to build the effective medications.

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