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Progress of Research on the Clinical Application of Radiation Protection Agents

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Abstract

With the advancement of nuclear technology, there is an increasing exposure of individuals to ionizing radiation. Incidents of radiation exposure occur occasionally, with the risk of radiation damage continuously rising. Radiation protectants are employed to prevent, alleviate, and treat ionizing radiation injuries. However, many current radiation protectants exhibit potent side effects, and there is currently no clinically established radiation protectant in routine use. Researchers have persistently endeavored to explore effective and low-toxicity radiation protectants. This article primarily focuses on internationally approved radiation protectants such as amifostine, dexrazoxane, phosphoramide mustard, polyethylene glycol-conjugated phosphoramide mustard, and sargramostim. Additionally, it discusses some natural antioxidants, resveratrol, and mesenchymal stem cells, which are currently undergoing clinical trials and promising to offer new avenues for the prevention and treatment of radiation injuries.

Keywords

Ionizing radiation, radiation damage, radiation protective agents, injury treatment

1. Introduction

With the advancement of nuclear energy and applications of nuclear technology, the potential risks of radiation exposure have significantly increased. These risks encompass scenarios such as nuclear radiation accidents, space exploration, radiation therapy, and radiation processing. Acute Radiation Syndrome (ARS) is a severe illness that manifests in individuals exposed to high doses of radiation over a short period, impacting the entire body or a substantial portion thereof. Instances of elevated radiation doses, as seen in nuclear accidents, cancer treatments, and diagnostic radiology, may result in symptoms of acute radiation sickness, affecting systemic health including cardiovascular, nervous, hematopoietic, and gastrointestinal systems (Mishra, Moftah, & Alsbeih, 2018).

Ionizing radiation detrimentally affects organisms primarily through indirect effects mediated by the generation of free radicals from ionization and direct impacts from radiation energy transfer, causing damage to biological macromolecules such as DNA, proteins, and lipids. The abundance of free radicals produced by water during certain doses of radiation can impair cellular membrane systems, leading to injuries in the immune, reproductive, nervous, and cardiovascular systems, and potentially instigating various common diseases or even carcinogenesis. To mitigate and prevent the harmful effects of nuclear radiation incidents on human health, research into radiation damage prevention and treatment methods, along with the search for effective radioprotective agents, has become an urgent priority (Singh & Seed, 2017).

Over several decades, extensive research has been conducted on various compounds, natural products, and biologics for their radioprotective properties, yielding significant progress. Noteworthy among these is the thiophosphate compound amifostine (WR-2721), approved by the U.S. Food and Drug Administration (FDA) and clinically utilized in pre-radiotherapy regimens for cancer patients. However, its clinical application is limited due to substantial drug-related side effects.

Natural compounds such as plants and medicinal herbs are widely utilized in medicine for their minimal toxicity, cost-effectiveness, oral administration capability, and ability to exert effects through various mechanisms including immune and hematologic systems regulation. Studies have identified them as promising radioprotective agents (Obrador, Salvador, Villaescusa, et al., 2020). Mesenchymal stem cells (MSCs), a type of adult stem cell known for their self-renewal and multipotent differentiation potential, have gained increasing attention due to their attributes including multilineage differentiation, hematopoietic support, facilitation of stem cell engraftment, immune modulation, and self-renewal (Gao, Peng, Shan, et al., 2019). Current treatments for acute radiation syndrome primarily involve supportive therapies such as blood transfusion, fluid replacement, electrolyte management, and antibiotics. Biological agents like cytokines, growth factors, and MSCs are garnering significant interest in clinical radiation injury treatment for their ability to modulate the immune system, secrete hematopoietic growth factors, and reconstruct hematopoietic microenvironments, offering advantages such as low immunogenicity and ease of genetic transfection and expression. The application of MSCs in the clinical treatment of acute radiation injury holds considerable promise. This paper will provide a brief overview of the rapidly developing natural compound radioprotectors, biologics for radiation therapy, and potential protective mechanisms in recent years.

2. Listed Radiation Protectants

2.1 Aminophilin

Amifostine is an aminothiol compound with a terminal thiol moiety linked to a phosphorothioate group. Initially identified as S-2-(3-aminopropylamino)ethylphosphorothioate (WR-2721) among over 4400 compounds screened by researchers at the Walter Reed Army Institute of Research, it later gained recognition as amifostine, a molecular protector with significant market potential. Approved in 1994 as

a protective agent against space radiation for American astronauts, it received FDA approval for clinical use in 1996. Its application in clinics focuses on safeguarding salivary glands of patients undergoing high-dose head and neck radiation therapy, alleviating acute oral syndromes. Moreover, within the European Union, amifostine has been sanctioned for this indication, albeit its development and usage are hindered by notable side effects, including hypotension, nausea, vomiting, drowsiness, allergic dermatitis, fever, and shock.

2.2 Ulinastatin

Ulinastatin is a pancreatic enzyme inhibitor with a molecular weight of 67 kDa, initially purified from human urine, now widely employed in therapeutic research for acute sialadenitis and circulatory failure. Due to its ability to suppress the release of inflammatory mediators and improve microcirculation and signaling pathways, pretreatment with ulinastatin before radiotherapy can intercept the signaling pathway of Transforming Growth Factor-β (TGF-β), thereby mitigating pulmonary damage caused by radiotherapy. Concurrently, administering high doses of ulinastatin prior to radiotherapy can reduce inflammatory reactions and inhibit pulmonary fibrosis. This is primarily due to TGF-β's impact on fibroblasts, macrophages, and alveolar epithelial cells, regulating cell proliferation, anti-inflammatory effects, and maintaining extracellular matrix stability. However, the optimal therapeutic dose of ulinastatin exhibits significant toxicity, thereby limiting its widespread use.

2.3 Fegestrin and Polyethylene Glycol Fegestrin

Neupogen, formally known as filgrastim, is a granulocyte colony-stimulating factor designed to sustainably increase leukocyte counts. It has been approved by the US FDA for treating neutropenia in patients suffering from hematopoietic acute radiation syndrome (H-ARS) or gastrointestinal acute radiation syndrome (GI-ARS) resulting from radiation accidents. Studies such as those by MacVittie et al. (2015) have documented Neupogen's ability to enhance survival rates in rhesus monkeys with only 5% marrow function remaining post-irradiation. However, premature administration of Neupogen in monkeys with GI-ARS has shown increased mortality rates. Across various radiation exposures, Neupogen administration significantly enhances survival rates and accelerates neutrophil recovery in irradiated animals. Currently, Neupogen has demonstrated notable clinical benefits in several radiation accident victims.

Pegylated filgrastim, marketed as Neulasta, is a pegylated form of filgrastim with a longer half-life. Neulasta operates similarly to Neupogen but exhibits prolonged pharmacokinetics. It is also FDA-approved for ARS treatment. Studies involving miniature pigs with H-ARS have shown reduced mortality rates and decreased duration and severity of neutropenia following Neulasta administration, accompanied by a notable decrease in significant bleeding events (Legesse, Kaur, Kenchegowda, et al., 2019). Neulasta has also been utilized effectively in several radiation accident victims. However, both Neupogen and Neulasta carry a risk of delayed acute respiratory distress syndrome, necessitating vigilant monitoring of patient vital signs when administered (Singh & Seed, 2021).

2.4 Sargistane

The product Sandostatin is branded as Leukine, which is a recombinant human granulocyte-macrophage colony-stimulating factor expressed in yeast. Leukine is capable of promoting the proliferation, differentiation, and maturation of various myeloid cells, thereby aiding in the treatment of bone marrow suppression caused by radiation.

In 2018, Sargistane was approved by the US FDA for the treatment of H-ARS. Research has shown that treatment with Sargistane significantly improves survival rates in rhesus macaques uniformly irradiated for 24 hours, with markedly increased minimum levels and earlier recovery times of neutrophils, leukocytes, and lymphocytes (Clayton, Khan-Malek, Dangler, et al., 2020).

3. Plant and Cellular Natural Ingredients Radiation Protectors

3.1 Resveratrol

Resveratrol (trans-3,5,4'-trihydroxystilbene) is a naturally occurring polyphenolic compound, primarily found in plants such as grapes, peanuts, and mulberries. In vitro, resveratrol exhibits potent antioxidant abilities, significantly enhancing antioxidant enzymes like superoxide dismutase, catalase, glutathione peroxidase, and non-enzyme antioxidants such as reduced glutathione, vitamin C, vitamin E, and β-carotene. It also reduces lipid peroxidation levels, scavenges and inhibits the production of free radicals, and demonstrates anti-inflammatory and anticancer effects (Cecerska-Heryć, Wiśniewska, Serwin, et al., 2024). Resveratrol regulates lipid metabolism, inhibits lipoprotein synthesis, and slows platelet aggregation, playing a crucial role in preventing human cardiovascular diseases. It induces activation of cystathionine gamma-lyase and other molecular signals, including CD95, mitogen-activated protein kinase, and Bcl-2, to promote cancer cell apoptosis. Specific mechanisms may involve inducing apoptosis, regulating the cell cycle, inhibiting angiogenesis, and suppressing NF-κB and cyclooxygenase pathways. Carsten et al. (2008) have reported on resveratrol's radioprotective effects, primarily inducing apoptosis, scavenging radiation-induced free radicals, inhibiting lipid peroxidation, and causing cell cycle arrest, thereby exerting antioxidant effects widely applicable in disease prevention and treatment. However, resveratrol exhibits significant toxicity, limited absorption through oral routes, and rapid metabolism in the intestines and liver, hindering its bioactivity and restricting its applications.

3.2 Goldfinch Isoflavin

Genistein, an isoflavone derived from soybeans, operates with mechanisms that remain incompletely elucidated. Research suggests that Genistein may function partially through GPER1 and potentially modulate hematopoietic progenitor cell numbers by enhancing cell cycle checkpoints and DNA repair enzyme expression (Landauer, Harvey, Kaytor, et al., 2019). Due to its poor aqueous solubility, oral bioavailability of Genistein is markedly limited. Humanetics has developed Genistein nanoparticles named BIO 300, administered intramuscularly 24 hours before radiation exposure, significantly increasing bone marrow cell count in irradiated mice (Singh & Seed, 2020). Studies also indicate that

Genistein alleviates radiation-induced impairments in mice (Jackson, Pavlovic, Alexander, et al., 2019). Currently, BIO 300 holds orphan drug status from the US FDA and is undergoing Phase I clinical trials.

3.3 Vitamin C

Administering pharmacological doses of ascorbic acid through intravenous infusion to achieve plasma vitamin C levels greater than 20 mmol/L (Schoenfeld, Alexander, Waldron, et al., 2019). Pharmacological doses of ascorbic acid can arrest cells in the S phase, where cells exhibit increased resistance to radiation (Alexander, Wilkes, Schroeder, et al., 2018). However, protective effects are only demonstrated with intravenous administration, possibly due to the ability to bypass intestinal transport proteins, leading to higher plasma drug concentrations. Currently, pharmacological doses of ascorbic acid have entered Phase IIA clinical trials, demonstrating good safety and tolerability (Polireddy, Dong, Reed, et al., 2017).

3.4 HemaMax TM

HemaMax TM is a recombinant form of human IL-12. IL-12 functions by releasing EPO and enhancing IFN-γ levels, promoting hematopoietic, immune, and gastrointestinal function restoration in irradiated animals. Administration of HemaMax TM 24 hours post whole-body irradiation has shown to increase mouse survival rates from 0% to 60% (Basile, Ellefson, Gluzman-Poltorak, et al., 2012). Currently, HemaMax TM has completed phase I and II clinical trials, with results yet to be disclosed.

3.5 Hematopoietic Stem Cells

Hematopoietic stem cells refer to precursor cells of erythrocytes, platelets, granulocytes, monocyte-macrophages, dendritic cells, mast cells, and osteoclasts. Studies have indicated that hematopoietic stem cells can enhance survival rates in irradiated mice, even at lethal doses, underscoring their therapeutic potential. Cellerant Therapeutics is advancing a composite of human hematopoietic stem cells for treating acute radiation syndrome (ARS), currently undergoing Phase I clinical trials (Singh, Romaine, & Seed, 2015).

4. Summary and Outlook

Ionizing radiation can significantly impact hematopoietic and immune systems. Exposure to doses exceeding 0.5 Gy can induce immune suppression. Acute Radiation Syndrome (ARS) resulting from high-dose ionizing radiation damage manifests as a complex syndrome affecting the blood, cardiovascular, nervous, and gastrointestinal systems. Supportive therapy for ARS primarily involves antiemetics, analgesics, blood transfusions, fluid replacement, and infection prevention and management. Currently, there is a lack of ideal radioprotective drugs. Ideal radiation protectants should ideally: 1) prevent or repair tissue and organ damage caused by radiation exposure, 2) provide protection whether administered before or after exposure, 3) act quickly with a long effective half-life, 4) be orally administered, 5) be convenient for storage and transport, 6) be resistant to radiation and high temperatures, and 7) be cost-effective. Therefore, the pursuit of broad-spectrum, efficacious, and

low-toxicity novel radioprotective and therapeutic drugs, utilizing natural components from plants and cellular factors such as cytokines and stem cells, represents a promising strategy in both research and application.

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