Chapter 9 – Medical Countermeasures to Radiation Exposure

10/31/2024

Outlines

- **Introduction and Definitions**
- Radioprotectors
- Radiation Mitigators
- Radiation Therapeutics/Eliminators
- Dietary Supplements as Countermeasures to Radiation

Classes of Countermeasure Drugs

Radiation Protectors

Prophylactic agents administered **prior to** radiation exposure to reduce the level of cellular or molecular damage

Radiation Mitigators

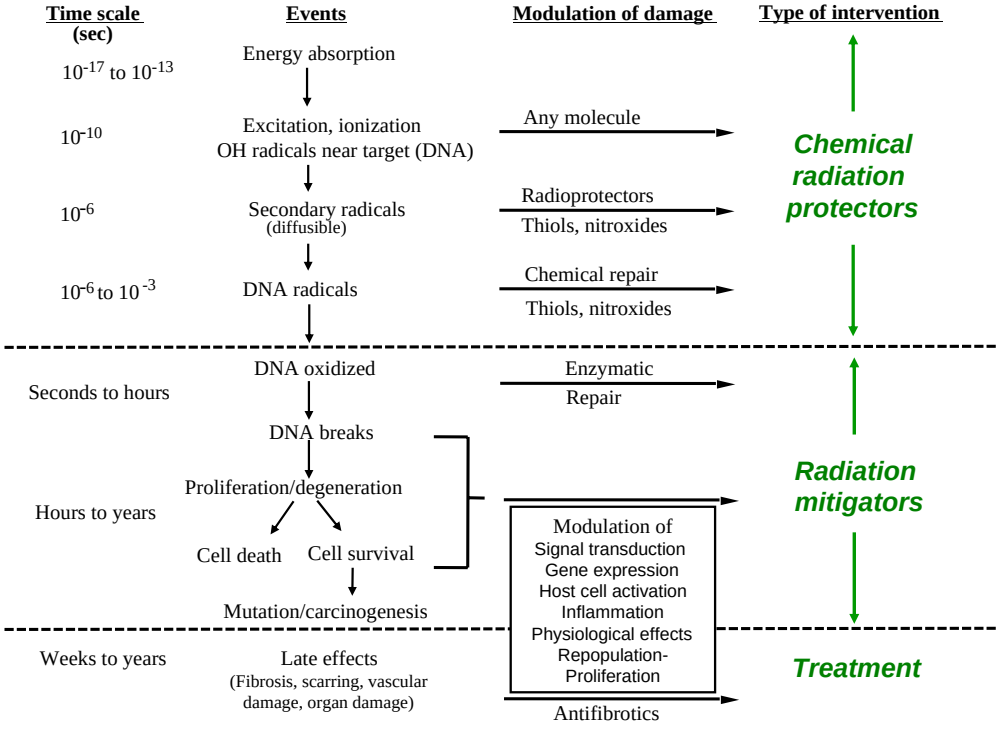
Drugs delivered *at the time of radiation* or *after* radiation, but **prior to the manifestation** of normal tissue toxicity, to reduce the severity of the radiation response

Radiation Therapeutics (Eliminators)

Agents given **after overt symptoms appear** in order to stimulate repair or regeneration (though the example given in the book doesn't follow this definition)

Critin 2010 – The oncologist 15: 360-371

Classes of Drugs



The Oncologist 2010;15:360 –371

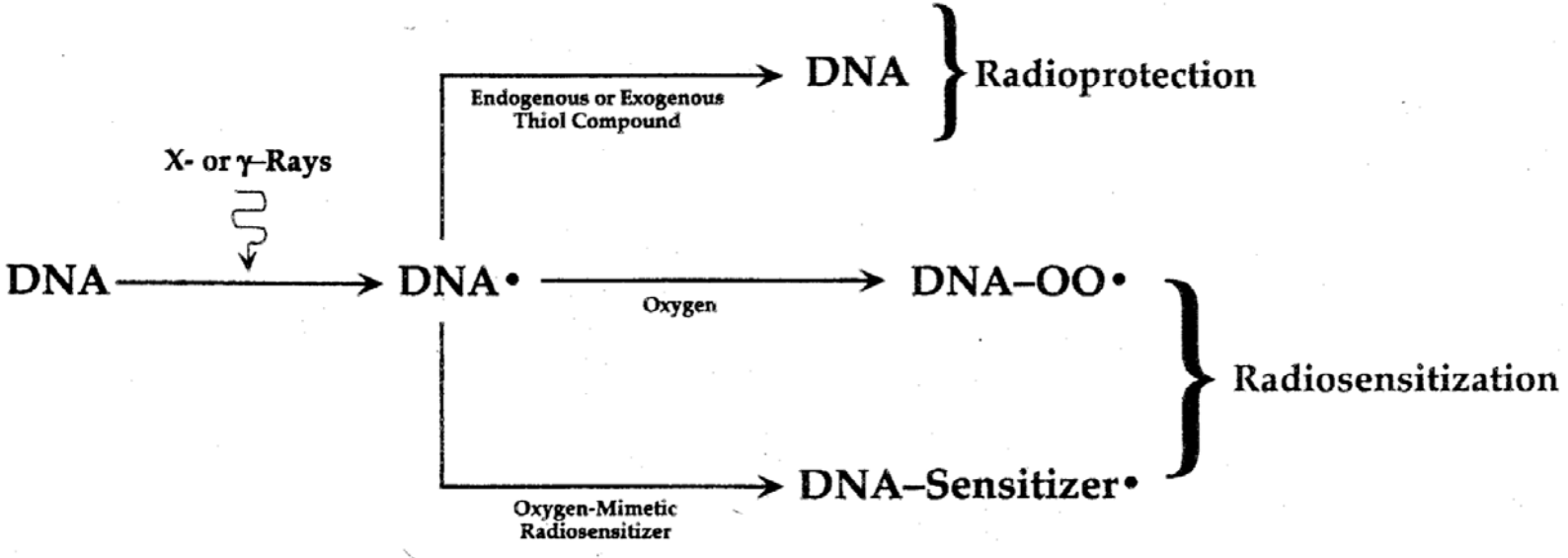
Outlines

Radiation Protectors

Prophylactic agents administered **prior to** radiation exposure to reduce the level of cellular or molecular damage

- Introduction and Definitions
- **Radioprotectors**
  - Cysteamine
  - WR-2721(Amifostine, only FDA-approved drug as a radioprotector)
  - Aminothiol (e.g., PrC-210)
- Radiation Mitigators
- Radiation Therapeutics
- Dietary Supplements as Countermeasures to Radiation

Radioprotection vs. Radiosensitization

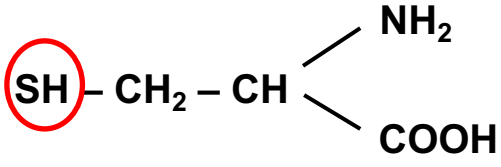


Radioprotectors

- Radioprotectors are chemicals that reduce the biological effects of radiation
- These were developed primarily by the military during the “cold war” years
- The most remarkable are the **sulfhydryl (SH) compounds**

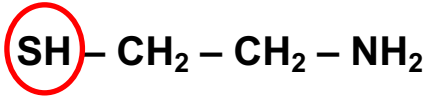
Sulfhydryl Compounds

Cysteine



Was found to protect mice from the effects of TBI if the drug was injected or ingested in large amounts before the radiation exposure

Cysteamine



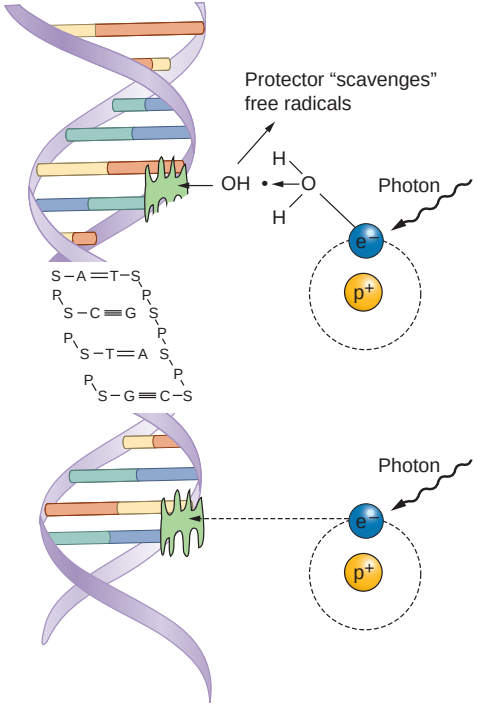
Animals injected with cysteamine requires 1.8 x the x-ray dose to produce the same mortality rate

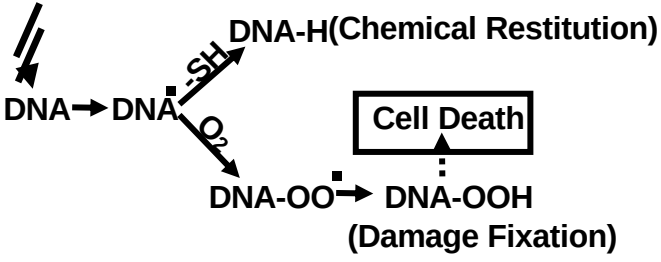
Structural features – a free SH group at one end of the molecule and a strong basic function at the other end, separated by a straight chain of 2 or 3 carbon atoms

Mechanism of Action of SH Compounds

- Free radical scavenging
- Hydrogen atom donation to facilitate direct chemical repair at sites of DNA damage
- Other factors not fully understood

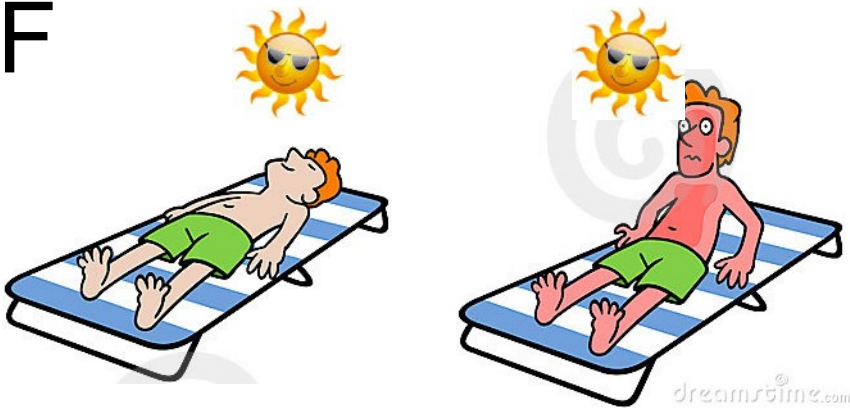
Mechanism of Action





Thus, SH compounds are most effective for **low LET radiations**!

SPF



SPF, or **Sun Protection Factor**, is a measure of how well a sunscreen will protect skin from UVB rays

If your skin would normally burn after **10 minutes** in the sun, applying an **SPF 15** sunscreen would allow you to stay in the sun without burning for approximately **150 minutes** (a factor of 15 times longer).

Dose-Reduction Factor (DRF)

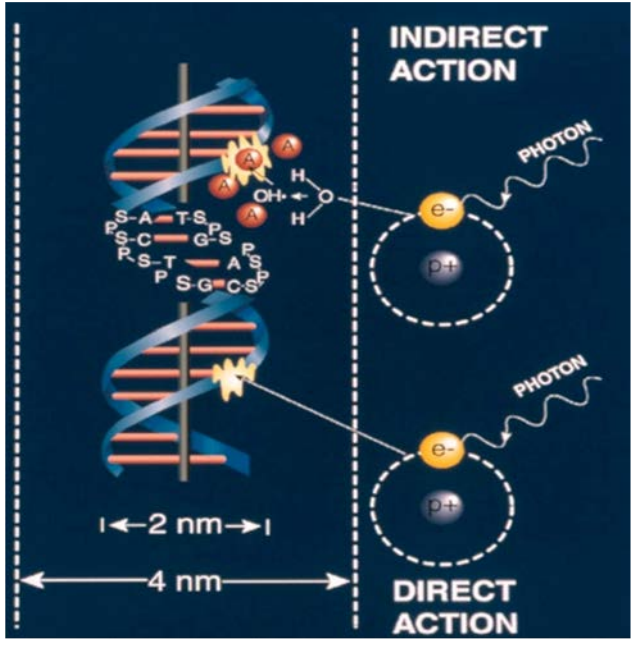
$$\text{DRF} = \frac{\text{Dose of radiation in the presence of the drug}}{\text{Dose of radiation in the absence of the drug}}$$

to produce a given level of lethality

Note that this definition is analogous to that of OER, and SPF

What is the largest possible value of DRF for sparsely ionizing radiation?

DRF



Recall that for low LET radiation, 2/3 biological damage is via **indirect action**

With effective scavenging of all free radicals, the largest possible value of DRF would equal the oxygen enhancement ratio, with a value of **2.5-3.0**

SH Radioprotectors in Practice

- Cysteine and cysteamine are toxic at the doses required for good protection
- Over 4,000 alternative forms of SH compounds have been tested
- Most promising seem to be those that have the SH group covered by a phosphate (PO_3) group

Effect of Adding a PO_3 Group

Beta-mercaptoethylamine

Drug	Formula	Mean 50% Lethal Dose (Range) in Mice	Dose-reduction Factor
MEA	$NH_2–CH–CH_2–SH$	343 (323–364)	1.6 at 200 mg/kg
MEA-PO_3	$NH_2–CH_2–CH–SH_2PO_3$	777 (700–864)	2.1 at 500 mg/kg

Reduced toxicity allows a higher concentration to be used, and therefore an increased LD_{50} and DRF

Once the PO_3 group is stripped by alkaline phosphatase, the free SH group can scavenge free radicals

Radioprotectors in Practice

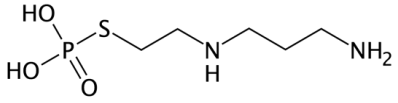
Compound	Structure	Use
WR-638	$NH_2CH_2CH_2SPO_3HNa$	Carried in field pack by Russian army (cystaphos)
WR-2721	$NH_2(CH_2)_3NHCH_2CH_2SPO_3H_2$	Protector in radiotherapy and carried by US astronauts on lunar trips (amifostine)
WR-1607	$CH_3(CH_2)_9NHCH_2CH_2SSO_3H$	Marketed as rat poison (d-CON)

GI and BM Protection in Mice

Compound	Drug Dose, mg/kg	Dose-reduction Factor	
		7 Days **(GI death)**	30 Days **(BM death)**
WR-638	500	1.6	2.1
WR-2721	900	1.8	2.7
WR-1607	10	—	2.1

Approaches the theoretical max value of 3

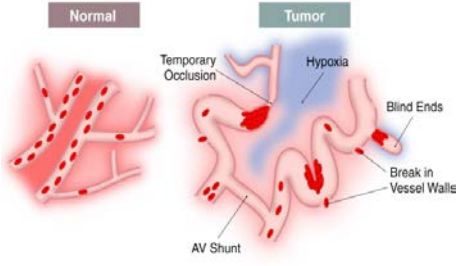
Amifostine (WR-2721)



- Amifostine is a phosphorothioate
- It is nonactive and does not readily permeate cells
- Converted to active metabolite (WR-1065) by alkaline phosphatase, which readily enter the cell
- It is therefore a “**prodrug**”

Amifostine – Rationale for Clinical Use

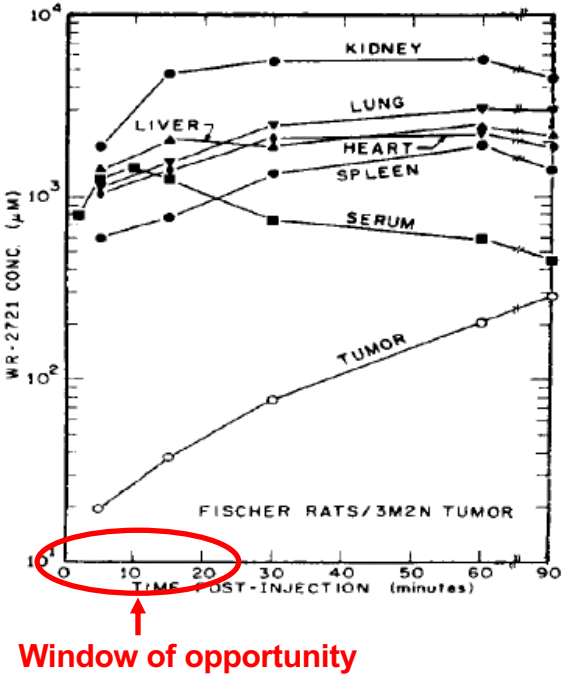
- In animal studies, amifostine quickly floods normal tissues but penetrate more slowly into tumors (due to poor vasculature)



- If the radiation is given within minutes after the administration of amifostine, there is a differential sparing of normal tissue compared with tumor cells
- Additional selective factors are attributed to acidosis of tumors, and the lower expression of alkaline phosphatase

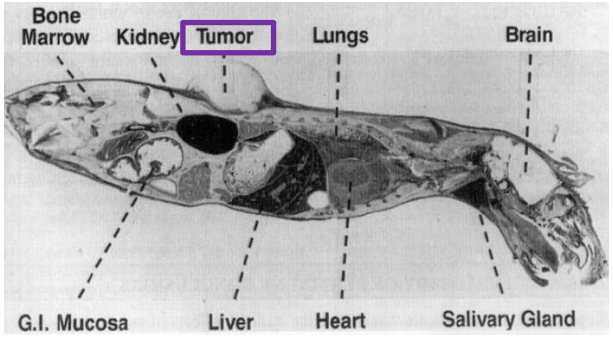
Amifostine – Animal Studies

Intraperitoneal injection of amifostine



Window of opportunity

Autoradiograph of a mouse 6 mins after injection of S-35 labeled amifostine



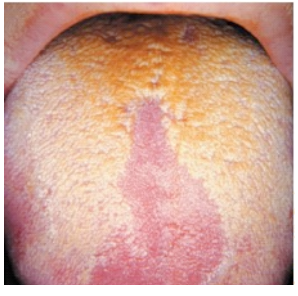
Tissues Protected[a]	Tissues not Protected
Bone marrow (2.4–3)	Brain
Immune system (1.8–3.4)	Spinal cord
Skin (2–2.4)	
Small intestine (1.8–2)	
Colon (1.8)	
Lung (1.2–1.8)	
Esophagus (1.4)	
Kidney (1.5)	
Liver (2.7)	
Salivary gland (2.0)	
Oral mucosa (>1)	
Testes (2.1)	

BBB

Amifosine – Clinical Application

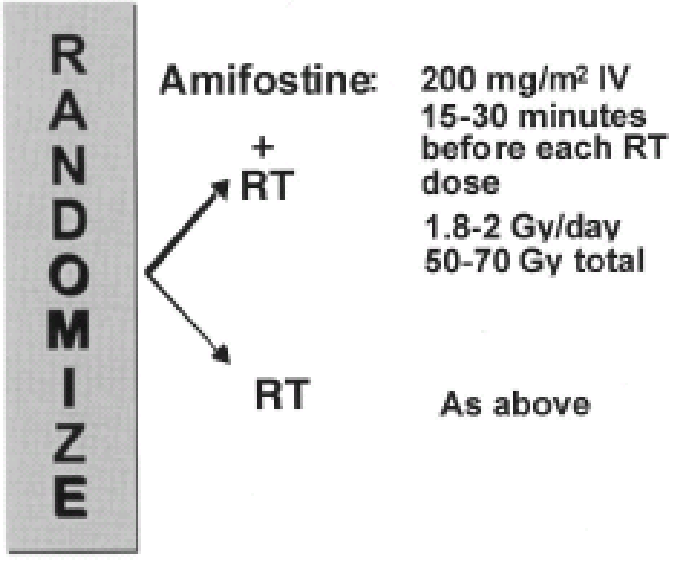
- Sold under the trade name Ethyol

- FDA approved for use in prevention of xerostomia (dry mouth) via sparing of the salivary gland in patients treated for H&N cancer in the post-op setting



- Major complication = hypotension

Amifostine – RTOG Trial

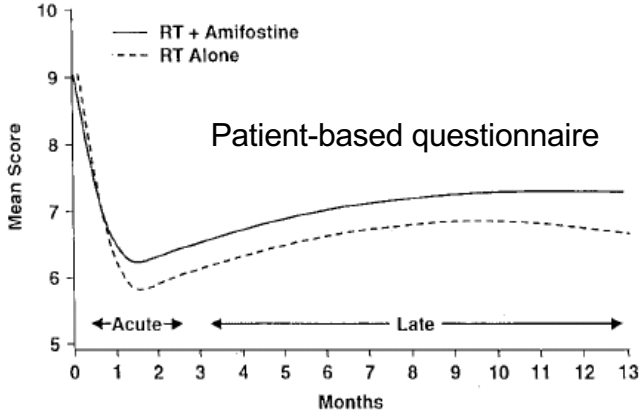


315 patients with H&N cancer enrolled

Toxicity – patients receiving Amifostine experienced significantly more frequent nausea, vomiting, hypotension and allergic reaction

Brizel 2000

Amifostine – RTOG Trial

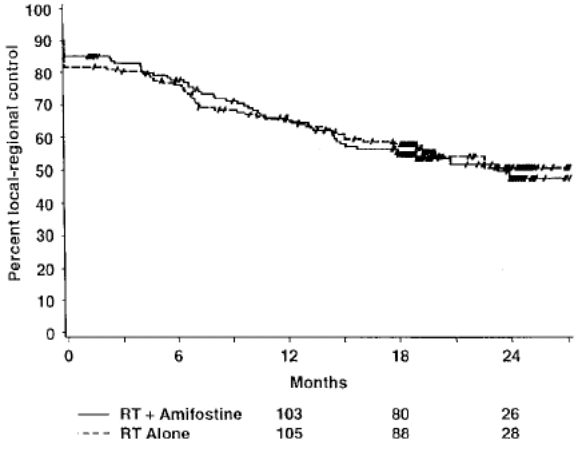


Gastrointestinal disorders			
	Grade		
Adverse Event	1	2	3
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL
Definition: A disorder characterized by frequent and watery bowel movements.			
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min
Definition: A disorder characterized by reduced salivary flow in the oral cavity.			

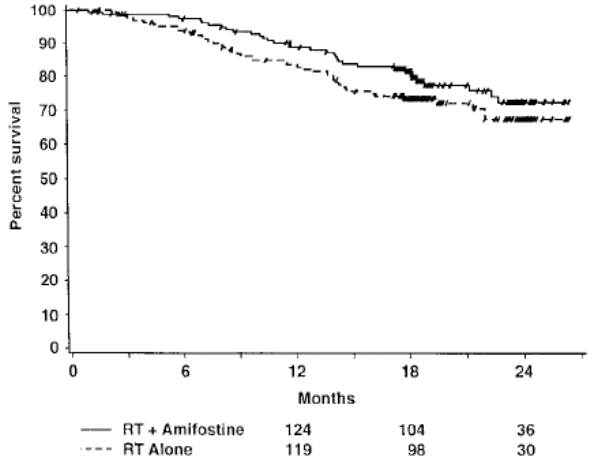
	Amifosine + RT	RT alone	p
Grade ≥ 2 acute xerostomia	**51%**	**78%**	**< 0.001**
Grade ≥ 2 late xerostomia	**34%**	**57%**	**0.002**

Conclusion – Amifostine significantly ↓ incidence of acute and late xerostomia

Amifostine – RTOG Trial



Locoregional control

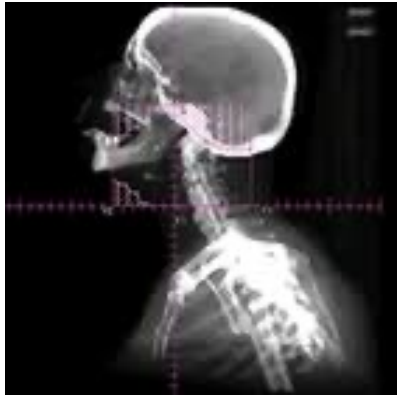


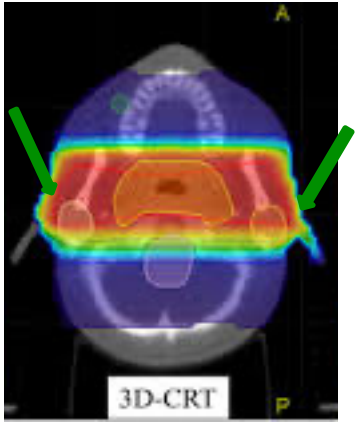
Overall Survival

Conclusion – Amifostine does NOT compromise the efficacy of radiotherapy

Salivary Gland Sparing in H&N RT

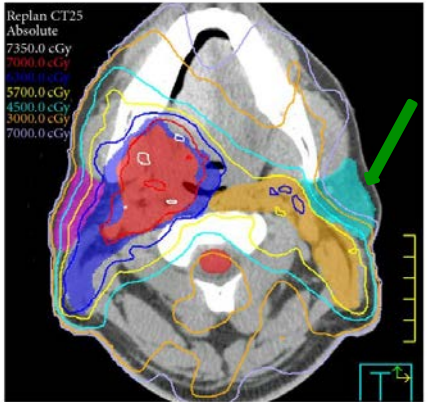
Rt and Lt lateral beams





Parotid gland receives full dose

IMRT



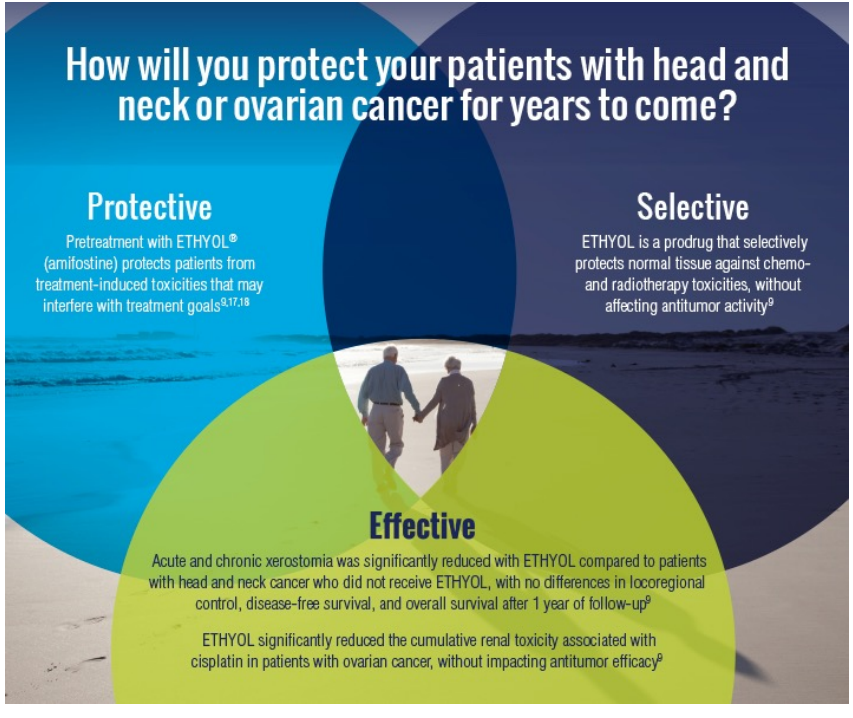
Contralateral parotid gland spared

Use of amifostine has fallen out of favor

Amifostine and Chemotherapy

- SH compounds may also be a protector for chemotherapy
- Reported to offer protection against nephrotoxicity, ototoxicity, and neuropathy from cisplatin and hematologic toxicity from cyclophosphamide
- No obvious protection against antitumor activity was seen

Amifostine – FDA Approved Indications



CUMBERLAND PHARMACEUTICALS

Clinigen Acquires Ethyol
Clinigen Acquires Ethyol
20 Aug 2014

Clinigen Group and Cumberland Pharmaceuticals launch Ethyol® in the U.S.
Clinigen Group and Cumberland Pharmaceuticals launch Ethyol® in the U.S.
26 Sep 2016

Clinigen to assume control of US commercial rights of Ethyol® and Totect® by Q4 2019
Clinigen to assume control of US commercial rights of Ethyol® and Totect® by Q4 2019
15 May 2019

INDICATION:
ETHYOL® (amifostine) is indicated to reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer.

ETHYOL is indicated to reduce the incidence of moderate to severe xerostomia in patients undergoing post-operative radiation treatment for head and neck cancer, where the radiation port includes a substantial portion of the parotid glands.

References:
1. ETHYOL [prescribing information]. Nashville, TN; Cumberland Pharmaceuticals Inc.; May 2017. **2.** Brizel DM, Wasserman TH, Henke M, et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. *J Clin Oncol.* 2000;18(19):3339-3345. **3.** Wasserman TH, Brizel DM, Henke M, et al. Influence of intravenous amifostine on xerostomia, tumor control, and survival after radiotherapy for head-and-neck cancer: 2-year follow-up of a prospective, randomized, phase III trial. *Int J Radiat Oncol Biol Phys.* 2005;63(4):985-990.

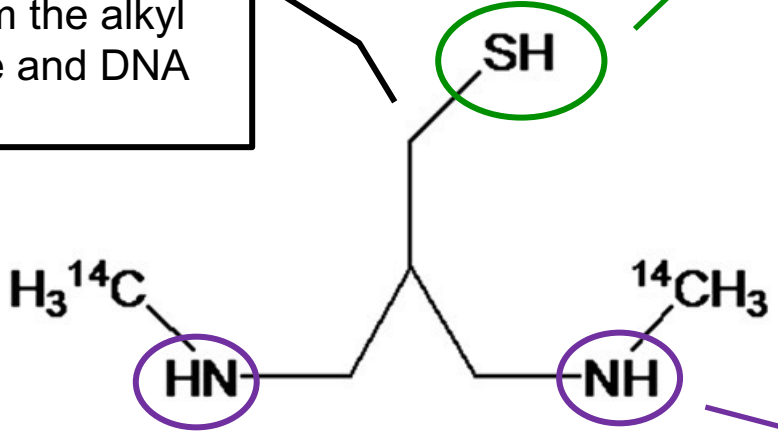
Amifostine – Other Uses

- Amifostine also protect against radiation-induced mutagenesis
- Antimutagenic effect is seen at dose as low as 25 mg/kg (vs. 400 mg/kg for cytoprotection)
- Antimutagenic effect is also seen if the drug is added 3 hours after irradiation
- Possible mechanism – due to polyamine-like properties which stabilizes DNA-damaged sites and promote error-free repair

New Radioprotectors – Aminothiol

A free thiol ROS scavenging group

A side chain that displaces the thiol away from the alkyl backbone and DNA helix



A short, flexible alkyl backbone with 2 charged amines for strong ionic interaction with DNA

PrC-210

Small size allows efficient transmembrane diffusion

PrC-210

Biology Contribution

A New Orally Active, Aminothiol Radioprotector-Free of Nausea and Hypotension Side Effects at Its Highest Radioprotective Doses

Cheryl M. Soref, Ph.D.,* Timothy A. Hacker, Ph.D.,† and William E. Fahl, Ph.D.*,‡

International Journal of Radiation Oncology biology • physics

Radioprotection

PrC-210 in water (200 mL) was administered by gavage to rats and mice 15-90 min before irradiation (9.0 Gy), and survival was assessed through the subsequent 60 days

Oral PrC-210 conferred 100% survival in rat and mouse models against an otherwise 100% lethal whole-body radiation dose (9.0 Gy).

Toxicity

After a SC injection of PrC-210, amifostine, or loperamide, ferrets were returned to the observation box and digitally videotaped for retching or emesis

No retching or emesis in 10 ferrets treated with PrC-210 and no induced hypotension in arterial cannulated rats treated with PrC-210

Int J Radiation Oncol Biol Phys, Vol. 82, No. 5, pp. e701–e707, 2012

Outlines

Radiation Mitigators

Drugs delivered *at the time of radiation* or *after* radiation, but **prior to the manifestation** of normal tissue toxicity, to reduce the severity of the radiation response

- Introduction and Definitions
- Radioprotectors
- **Radiation Mitigators**
  - Neupogen, Neulasta, Leukine (mitigate marrow toxicity)
  - Palifermin (Keratinocyte growth factor)
- Radiation Therapeutics
- Dietary Supplements

Radiation Mitigator

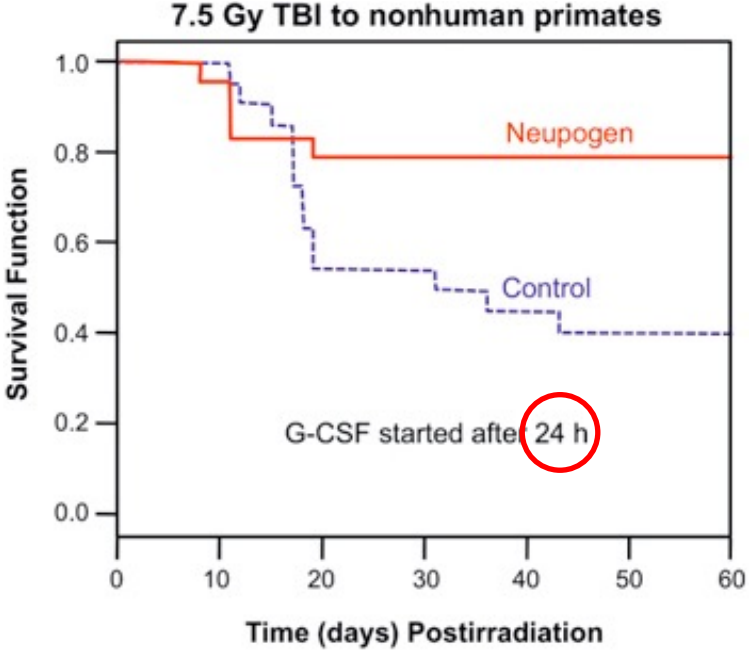
- Radiation mitigators can be agents delivered during or shortly after exposure to repopulate a critical cell compartment such as the bone marrow or mucosa
- Exposure to radiation at moderate doses causes a profound decrease in cells in the bone marrow and places patients at risk of death from infection or bleeding
- **Cytokines** and **growth factors** may promote recovery by stimulating the repopulation of neutrophils and thrombocytes in the bone marrow

Radiomitigator – Hematopoietic ARS

- Two **radiomitigators** for hematopoietic ARS, **Neupogen** and **Neulasta**, have been approved by the FDA through repurposing
- **Neulasta** and **Neupogen** are both made of a natural protein known as granulocyte-colony stimulating factor (or "G-CSF").
  - Neulasta has a polyethylene glycol, "PEG," unit added to it, which makes the molecule larger so that it stays in body system longer than Neupogen
- **Leukine** is a GM-CSF, which stimulates both granulocytes and macrophages

Singh 2018 – Journal of Radiation and Cancer Research; 9(1): 17-23

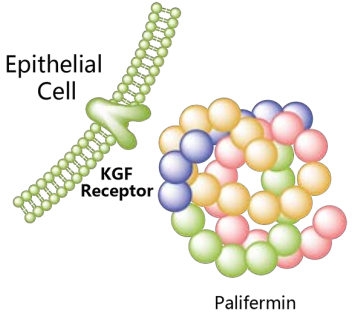
Radiomitigator – Hematopoietic ARS



Neupogen, Neulasta, and **Leukine**, have already been procured by the US government for the vendor-managed inventory

Radiomitigator – Oral Mucosa

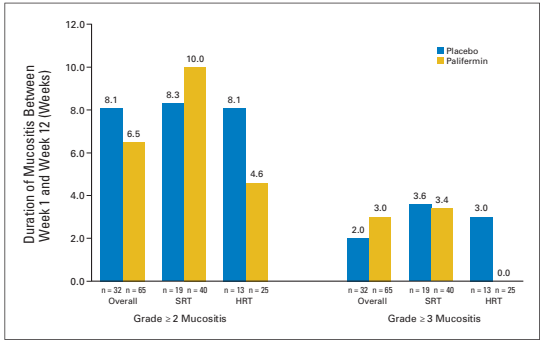
- **Keratinocyte growth factor (KGF)** stimulates a number of cellular processes such as differentiation, proliferation, DNA repair, and detoxification of reactive oxygen species
- These properties make KGF an attractive method to stimulate the recovery of mucosa after ionizing radiation
- Delivery of KGF in *animal models* prevents radiation-induced xerostomia and mucositis

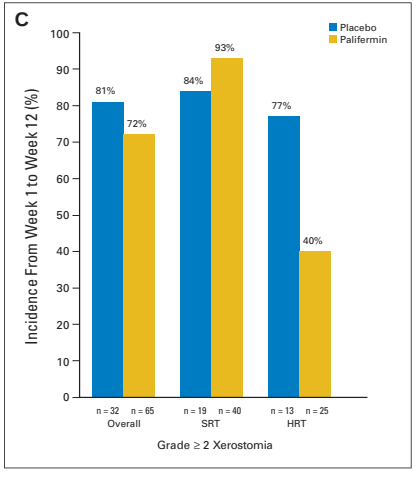


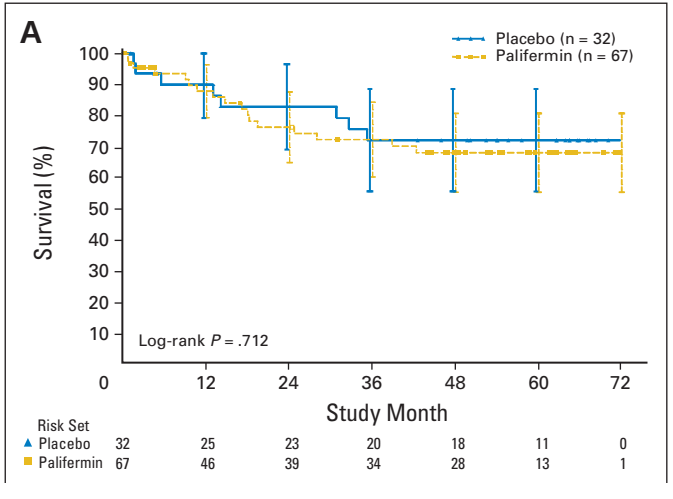
Palifermin is a recombinant human KGF that is approved for use in ↓ the incidence and duration of severe oral mucositis in patients with hematologic malignancies who receive high doses of chemotherapy and radiation therapy followed by stem cell rescue

Radiomitigator

~ 100 H&N pts treated with concurrent chemoRT
Palifermin was administered by IV bolus injection once a week x 10 doses







No difference in duration of grade ≥ 2 mucositis
Palifermin ↓ mucositis, dysphagia, xerostomia during hyperfx RT, but not standard RT

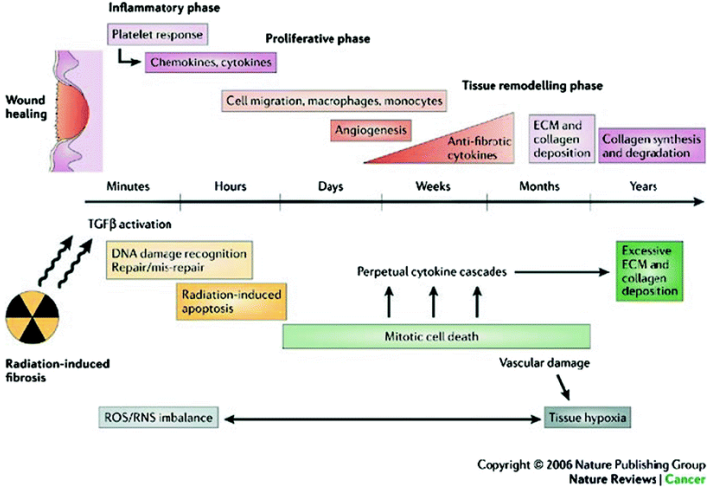
Brizel 2008; JCO: 26:2489-2496

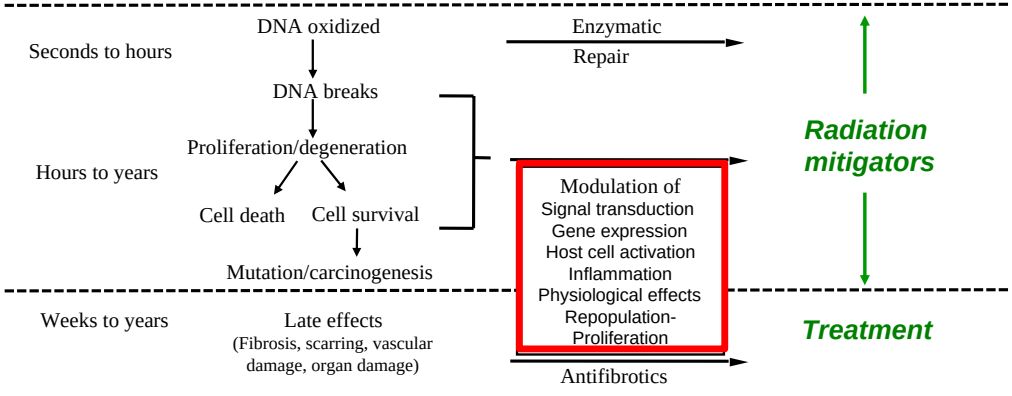
Radiomitigator – **Late** Tissue Toxicity

- Radiation-induced late normal tissue toxicity is increasingly being appreciated as a phenomenon of ongoing changes in tissue after radiation but prior to the manifestation of toxicity
- These events include ongoing mitotic cell death and perpetually active cytokine cascades that can lead to vascular damage, tissue hypoxia, and excessive extracellular matrix deposition
- Radiation mitigators aim to interrupt these cascades or intervene to prevent the perpetuation of damage and thus reduce the expression of toxicity

The Oncologist 2010;15:360 –371

Radiomitigator – Late Tissue Toxicity





Outlines

Radiation Therapeutics (Eliminators)

Agents given **after overt symptoms appear** in order to stimulate repair or regeneration (though the example given in the book doesn't follow this definition)

- Introduction and Definitions
- Radioprotectors
- Radiation Mitigators
- **Radiation Therapeutics/Eliminator**
  - **Potassium Iodide**
  - **Prussian Blue**
  - **DTPA**
- Dietary Supplements as Countermeasures to Radiation

Radionuclide Eliminators

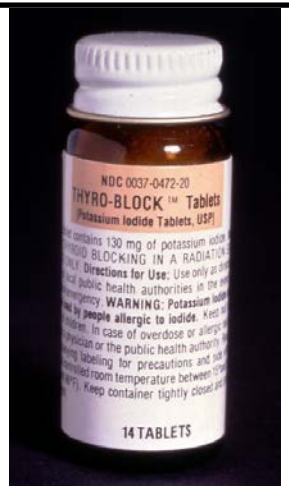
- In the event of an accident at a nuclear power facility, or a radiologic terrorist attack, there is the potential for members of the public to ingest radioactive materials that may have been released into the atmosphere
- **Radionuclide eliminators** are drugs that discorporate or block absorption of internalized radionuclides

Treatment of Internal Contamination

- Radionuclide-specific
- Most effective when administered early
- May need to act on preliminary information
- NCRP-65: “Management of Persons Accidentally Contaminated with Radionuclides”

Radionuclide	Treatment
Tritium	Forced water
Iodine	Potassium iodide
Cesium	Prussian blue
Iridium	Penicillamine
Plutonium	DTPA
Uranium	Bicarbonate

FDA Approved



Potassium Iodide – Iodine

- KI tablets flood the thyroid with nonradioactive iodine so that if **radioactive iodine** is ingested, it is less likely to be internalized in the thyroid
- This is especially important for children or for any individuals living in areas with low iodine contents, as was the case at Chernobyl

Potassium iodide supplies sold out in the US

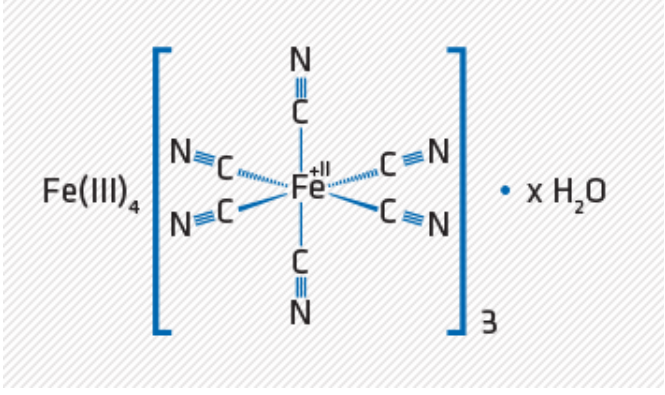
Radiation sickness drug stocks dwindle as Americans panic buy over fears of contamination from Japan

As Japan scrambles to contain a possible nuclear disaster, 5,000 miles away on the Pacific west coast Americans are busily doing what they do best - panicking.

The three US government-approved suppliers of potassium iodide, a drug used as a protection against radiation sickness, have all sold out after a run on stocks from anxious west coasters fearful that the nuclear discharge from Japan was heading towards them. So intense was the rush that one of the suppliers, Anbex Inc, had been cleaned out of its 10,000 packets of 14 tablets within 24 hours of the Japanese earthquake.

The fact that only minuscule amounts of radiation have been detected on the American west coast, and that potassium iodide can have serious side-effects, has done nothing to dissuade the hoarders.

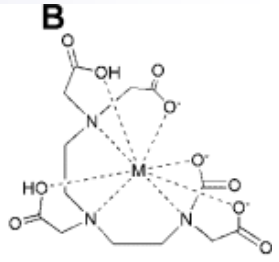
Prussian Blue – Cesium-137



Insoluble ferric hexacyanoferrate traps ingested radioactive cesium in the intestine so that it can be eliminated in the stools

The effectiveness of Radiogardase® was demonstrated in the 1987 Goiânia accident, the first extensive use of Prussian blue in the history of radiological accidents.
The Goiânia accident started when scavengers took and dismantled a **Cesium-137** teletherapy unit which Institute Goiâno de Radioterapia left at their old premises when they moved to a new one in 1985

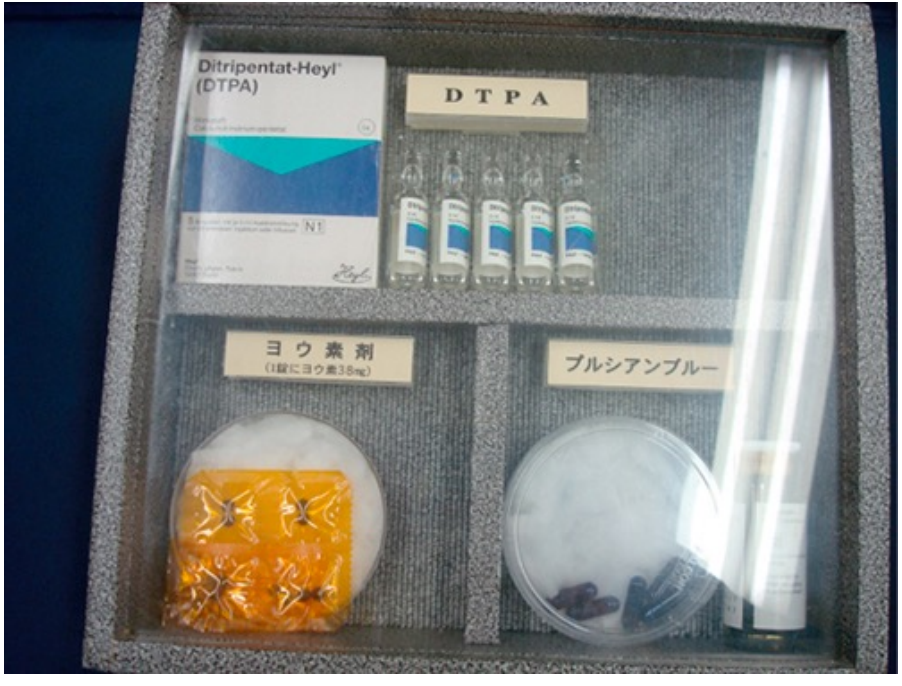
DTPA – Plutonium, Americium, Curium



DTPA

- Diethylenetriamine pentaacetic acid (DTPA) has high affinity for metal cations (chelator), routinely used in cases of heavy metal poisoning
- DTPA work by binding tightly to the radioactive plutonium, americium, or curium, which are then eliminated through urine
- Approved in 2004 by FDA for treatment of those who have breathed in (nebulizer) or otherwise been contaminated internally (IV injection) by **plutonium, americium,** or **curium**.

Radiation Therapeutics



A cabinet in the National Institute for Radiological Sciences in Chiba, Japan, containing an emergency supply of potassium iodide tablets, Radiogardase, and DTPA, used in the event of internalized radionuclides

For More Information

Literature regarding:

- Leukine Injection
- Neulasta Injection
- Neupogen Injection
- Calcium-DTPA Injection
- Zinc-DTPA Injection
- KI tablets and oral solution
- Radiogardase Capsules

https://www.fda.gov/drugs/emergencypreparedness/bioterrorismanddrugpreparedness/ucm063807.htm

Outlines

- Introduction and Definitions
- Radioprotectors
- Radiation Mitigators
- Radiation Therapeutics
- **Dietary Supplements as Countermeasures to Radiation**

Dietary Supplements as Countermeasures to Radiation

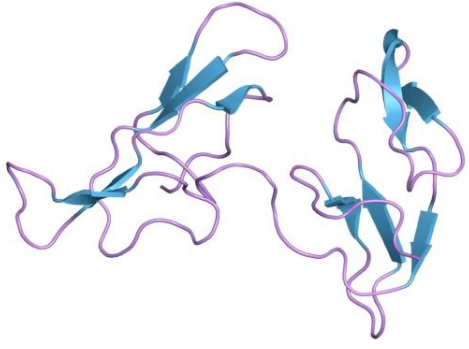
- Following 911 and the rise of nuclear terrorism threat, there has been a revived interest in the development of novel, effective, and nontoxic radioprotectors for potential use in homeland defense
- Dietary supplements involving antioxidants have a potential role

Bowman-Birk Inhibitor (BBI)

BBIs are a family of proteins which inhibit the proteolytic activities of trypsin, chymotrypsin, and elastase

They exhibit antioxidative activities and has long been proposed as a cancer chemopreventative agent

BBIs are primarily found in plants and in particular in the seeds of legumes, as well as in cereal grains



Antioxidants Cocktails

- L-selenomethionine
- Ascorbic acid
- N-acetyl cysteine
- Alpha-lipoic acid
- Vitamin E succinate
- Coenzyme Q10

Review Questions

Question 1

What is the definition of a radiation mitigator?

A. Agents delivered at the time of irradiation or after irradiation is complete with the intent preventing the manifestation of normal tissue toxicity
B. Agents delivered prior to irradiation with the intent of preventing or reducing damage to normal tissues
C. Agents delivered to ameliorate established normal tissue toxicity
D. Agents delivered at the time of irradiation with the intent preventing the manifestation of normal tissue toxicity
E. Agents delivered to increase the therapeutic ratio of clinical radiotherapy

Classes of Countermeasure Drugs

Radiation Protectors

Prophylactic agents administered **prior to** radiation exposure to reduce the level of cellular or molecular damage.

Radiation Mitigators

Drugs delivered *at the time of radiation* or after radiation, but **prior to the manifestation** of normal tissue toxicity, to reduce the severity of the radiation response

Radiation Therapeutics (Eliminator)

Agents given **after overt symptoms appear** in order to stimulate repair or regeneration

Critin 2010 – The oncologist 15: 360-371

Question 2

An agent which must be present at the time of irradiation to reduce normal tissue injury is called what?

A. A radiation sensitizer
B. A radiation mitigator
C. A radiation protector
D. An antifibrotic
E. A radiation mimetic agent

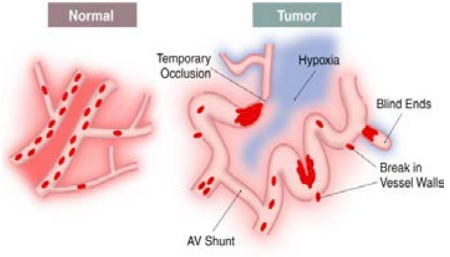
Question 3

Amifostine selectively radioprotects normal tissue by which mechanism(s)?

A. Scavenging free radicals
B. Selective uptake in normal tissues compared to tumor tissues
C. Reduction of oxygen tension in normal tissues
D. Stabilizing oxygenated hemoglobin
E. A and B
F. A and D

Amifostine – Rationale for Clinical Use

- In animal studies, amifostine quickly floods normal tissues but penetrate more slowly into tumors (due to poor vasculature)



- If the radiation is given within minutes after the administration of amifostine, there is a differential sparing of normal tissue compared with tumor cells