Collection of Recorded Radiotherapy Seminars

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DRUG RADIATION INTERACTION
Radiation Sensitizers and Protectors

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Overview

- Therapeutic ratio
- Modes of drug-radiation interaction
- Characteristics of Radiation sensitizers
- Categories
- Halogenated pyrimidines
- Hypoxic cell sensitizers
- Bioreductive drugs
- Radiation protectors
- Other ‘protectors’
Radiotherapy – Cure vs Complications

DOSE (Gy)

RESPONSE

Complications

Radiosensitive tumour

Radioresistant tumour

Drug Radiation interaction
Therapeutic ratio

May be defined as cure rates for a given rate of complications

If there is increased response in tumours relative to normal tissue, then there is therapeutic gain with a radiosensitizer
Radiation Modifiers

• Many drugs can cause modification of cellular response to radiotherapy.
• Rapid advances in cellular and molecular biology has resulted in a whole host of new drugs which may be used with radiation, mainly as sensitizer
• Radiosensitizer
  – any agent that increases the sensitivity of cells to radiation
• Radioprotector
  – any agent that reduces the sensitivity of cells to radiation (reduces the biologic effect of radiation)
Potential advantages of drug-radiation interactions

• Synergistic
  – Prevent repair of radiation induced damage
  – Synchronizing cells into radiation sensitive phase & recruitment into cell cycle
  – Preventing repopulation
  – Reducing fraction of hypoxic cells
  – Sensitizing hypoxic cells

• Independent
  – direct cytotoxicity
Potential disadvantages of drug-radiation interactions

- Selecting chemo & radioresistant clones
- Inducing accelerated repopulation
- Normal tissue sensitization
- Systemic effect reducing patient’s tolerance to radiation
Tumour repopulation

Inhibition of repopulation

Enhanced repopulation

Inhibition of repopulation during concurrent chemotherapy and radiotherapy

Repopulation during radiation alone

Surviving fraction vs. Radiation dose fractions

Repopulation during radiation alone

Enhanced repopulation following induction chemotherapy

Surviving fraction vs. Radiation dose fractions
Nomenclature

• Interactive
  – Addition of a drug causes a change in radiation response slope
    - Enhancement (synergism) - radiosensitizer
    - Inhibition - radioprotector
    - Protection - radioprotector

• Non-interactive
  – Dose response slope is transposed (moved) without a change in shape
    - Additive
Drug Radiation Interaction

- Surviving fractions vs. Radiation Dose
- "Pure" Radiation Sensitiser

Drug Radiation interaction
4 types of interaction can be seen:

- **Additive**: no change in response slope
- **Enhancement**: response slope is steeper
- **Inhibition**: response slope is less steep
- **Protection**: response slope is shallow and surviving fraction is more compared to radiation alone
Modes of interaction

- Spatial Co-operation
- Independent cell kill
- Protection of normal tissue
- Enhancement of tumour response
Isobologram of Drug-Radiation interaction

**Figure 1** Schematic isobologram for combination of radiation and chemotherapeutic agent. The scales represent an isoeffective level.
Spatial co-operation

- Using radiotherapy & chemotherapy to target separate tumour sites
- Eg leukemia
  - Systemic chemotherapy
  - Prophylactic cranial irradiation
- “Non-interaction”
  - Chemo & RT act independently from each other at different sites.
Independent cell kill

- Radiation & chemotherapy are given at full doses
- Both modalities have tumour effects
  - Combined effect is additive or sub-additive, NOT supra-additive
  - Aim for drugs with differing toxicity from radiotherapy
    - Toxicity is usually the limiting factor in RT
Independent cell kill (2)

• Principles
  – Avoid anti-tumour antibiotics eg doxorubicin
  – Avoid drugs with recognised toxicity in tissue of interest
    – Eg Methotrexate and spinal cord
    – Cyclophosphamide and lung
  – Avoid concurrent treatment
### Normal tissue damage

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Interstitial</th>
<th>B/Marrow</th>
<th>Lung</th>
<th>Response</th>
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<tbody>
<tr>
<td>RT</td>
<td>-----</td>
<td>---</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Chemo</td>
<td>+</td>
<td>+++</td>
<td>----</td>
<td>++</td>
</tr>
<tr>
<td>Combined</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>++++</td>
</tr>
</tbody>
</table>

When adding drugs to radiation, we must be careful not to enhance organ specific damage beyond tolerance. If both radiation and drug cause organ specific damage, there is a risk of additive damage to the said organ.
## Normal tissue damage - time dependence

### Table 20.2 Lung damage in mice as a result of combined treatment with radiation and drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug administration*</th>
<th>Source**</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>Concurrent</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>−</td>
<td>+++</td>
</tr>
<tr>
<td>Actinomycin D</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Vincristine</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CCNU</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>cis-Platinum</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>−</td>
<td>+</td>
</tr>
</tbody>
</table>

+++ severe enhancement of lung damage; ++ moderate enhancement; + slight enhancement (doubtful significance); − no enhancement.

*Before = 7 – 28 days before radiation; after = 7 – 28 days after radiation.

RADIOSENSITIZERS
Objective of a radiation sensitizer

- To increase tumour response more than radiotherapy alone
  - For a given complication rate
  - Tumour response must be more than normal tissue toxicity
    - “therapeutic gain”
ENHANCEMENT OF TUMOUR RESPONSE

- Aim for supra-additive effect
  - Additive
    - $1 + 1 = 2$
  - Supra additive (synergistic)
    - $1 + 1 > 2$

- Problem
  - Easy to show if dose-response curve is linear
    - Difficult for non-linear mathematics
In a tissue system where the dose-response is linear, if Drug A increases response by a percentage, this would hold true anywhere along the response curve.

**Diagram:**

- **Tumour response** vs **Radiation dose**
- Point **D1** to **X**
- Point **X** to **D2**
- **Drug A** indicated with a dashed line and a 10% increase at each point.
As normal tissue complication rates follow a sigmoidal pattern, small changes in dose or radiation sensitivity may result in large increase in complications.

At the steep portion of slope, a 1Gy increase in dose may increase bone marrow complication from 10% to 90%.

In lung, the same 1Gy increase may increase the complications by 20%.
Non-linear dose response (2)

- Non-linear dose response may also falsely give the impression of an enhance radiation response.
- A small radiation dose may have a small cell kill due to the shoulder region.
- Larger doses results in quadratic ($\beta^2$) cell kill.
- Drugs given with this larger dose may suggest enhance radiation response when it actually does not exist.

Figure 20.4 A non-linear dose–response curve can give a spurious impression of supra-additivity. In this example (two simultaneous doses of radiation given to mammalian cells in tissue culture) the effect plotted on the ordinate is log(surviving fraction).
Enhancement Ratios

- Magnitude of the sensitizing effect of a drug for a given effect is given by the sensitizer enhancement ratio (SER):

  \[
  \text{SER} = \frac{\text{radiation dose without sensitizer}}{\text{radiation dose with sensitizer}}
  \]

- The Dose Modification Factor of a drug, is defined as the dose of radiation required to produce an effect without and with a drug

  \[
  \text{DMF} = \frac{\text{Dose}_{(\text{radiation})}}{\text{Dose}_{(\text{radiation} + \text{drug})}}
  \]

- If DMF = 1 No drug effect
  
  < 1 Protection
  
  > 1 Enhancement
The concept of DMF is similar to movement of the response curve by either radiation sensitizers or protectors.

\[
\text{DMF}_x = \frac{D_1}{D_2} > 1 \\
\text{DMF}_y = \frac{D_3}{D_4} < 1
\]
Time-dependence interaction

- Interaction of drug-radiation depends on sequencing
  - Effect may be seen with drug given before, during or after radiation
- Enhancement ratio (SER) varies
  - Sequence / timing
  - Drug(s)
Timing dependence of SER

- Addition of drugs at different time-points relative to radiation may have differing effects.
- Misonidazole is an enhancer of radiation of hypoxic cells.
  - Given 30 minutes before radiation shows a markedly increase in cellular sensitivity compared to 4 hours before radiation.

Figure 17.3 Local tumour control in C3H mouse mammary carcinomas measured 120 days after radiation.
Cell survival with 5-FU at different time points with RT
• maximal effect is seen when 5-FU is given with radiation.

Figure 20.6 A time-line for the interaction of 5-fluorouracil (5-FU) and X-radiation in the treatment of mouse leukaemia. Radiation was given at time zero; points to the left of zero are for drug before radiation; points to the right are for drug after radiation. From Vietti et al (1971), with permission.
Characteristics of an ideal radiation sensitizer

- Acts selectively in tumour compared to normal tissue
- Reaches tumour in adequate concentration
- Predictable pharmacokinetics for timing with radiation therapy
- Able to be administered with every radiation treatment in a standard regimen
- Minimal toxicity of the drug itself
- Manageable enhancement of radiation therapy
Potential mechanisms of action of Radiation Sensitizers

- Directly enhances DNA damage
- Decreases repair of radiation damage
- Redistribution of cell cycle
- Alters cell biochemical and molecular response to radiation
- Causes cell death by novel mechanism (e.g., apoptosis)
Categories of Radiation Sensitizer

1. Increase in Initial Damage:
   - DNA critical target for radiation damage – dsb lethal lesions
   - Some lesion are repairable eg SS DNA break
   - An agent that causes more initial damage to critical cellular targets would be expected to enhance radiation effects if repair systems become saturated
     - eg. halogenated pyrimidines
2. Repair Inhibition:

- Ability to repair radiation damage is a vital cellular function
  - Molecules that can chemically restore damaged molecules → reducing species
  - Molecules and systems that can recognize and repair damaged substrates through a set of complex and ordered reactions
  - Cellular systems that prevent damages before it occurs
- Because of the lack of specificity of most agents used presently, normal tissue may also be radiosensitized
- Hydroxyurea: shown to inhibit excision-repair of thymine dimers and single-strand DNA breaks induced by radiation
- Cisplatin: form DNA crosslinks – inhibit repair of radiation damage
- 5FU
- Gemcitabine
3. Cell-cycle Redistribution:

- Tumour growth is governed by
  - The fraction of cells within the tumour that are actively dividing (cycling vs quiescent cells)
  - The duration of the cell cycle
  - The cell loss factor
- Cells vary in their response to radiation as a function of their position in the cell cycle
- Radiosensitivity:
  - G2-M phase >> late S or early G1
- Paclitaxel: G2-M block
- Gemcitabine?

[Diagram showing cell cycle phases and drug effects]
To be useful – the drug should give differential effect between tumour and normal tissues (ie. increase the therapeutic ratio).

So far, only 2 types of sensitizers found practical use in clinical radiotherapy:

1. Hypoxic cell sensitizers – increase radiosensitivity of cells deficient in molecular oxygen.
   
   Differential effect: hypoxic cells occur mainly in tumours

2. Halogenated pyrimidines – degree of sensitization depends on amount of analogue incorporated.
   
   Differential effect: faster tumour cell cycling \(\rightarrow\) more drug incorporated into tumour than surrounding normal tissue
Halogenated Pyrimidines

- 5-iododeoxyuridine (IUdR) and 5-bromodeoxyuridine (BUdR)
  - very similar to normal DNA precursor thymidine
  - halogen substitute in place of methyl group
- The similarity is so close that they are incorporated into DNA chain in place of thymidine
- This substitution weakens the DNA chain, cells are more susceptible to damage by radiation (also UV light)

Increasing percentage of pyrimidine substitution will result in increasing radiosensitivity. Therefore drug needs to be given over several generation of cell for maximal sensitivity.
Halogenated Pyrimidines – clinical trials

• Rationale: tumour cells cycle more rapidly than normal cells – so more drug replaces tumour cell DNA → selective radiosensitization
• Trials began in 1970s
• Drug needs to be delivered by intra-arterial infusion into main vessel supplying neoplasm to be treated (because liver dehalogenates the drug)
• Most appropriate tumours:
  – high growth fraction and
  – high labelling index (indicators of cell division)
• Head and neck tumours selected: tumour response good but normal tissue damage unacceptable (? why)
Halogenated Pyrimidines – Toxicity and Efficacy

- Skin toxicity with BUdR – light-induced rash (photosensitivity)
- Not observed with IUdR
- Dose-limiting toxicity for both: myelosuppression esp. thrombocytopenia
- No benefit of BUdR in anaplastic astrocytoma

BUdR increases sensitivity to UV light, but not IUdR
EXPLOITING DRUG – RADIATION INTERACTION

• Therapeutic strategies
  – Concurrent
  – Alternating
  – Sequential
    – Neo-adjuvant
    – Adjuvant
Potential advantages of concurrent chemo-radiotherapy

- **Synergistic**
  - Prevent repair of radiation induced damage
    - Cisplatinum
    - Doxorubicin
  - Preventing repopulation
  - Reducing fraction of hypoxic cells

- **Independent**
  - direct cytotoxicity
CONCURRENT CHEMOTHERAPY

• Benefit
  – Cervical cancer
  – Oesophagus
  – Anal cancer (increase local control)
  – Head & neck (but increase toxicity)
  – SCLC (Spatial for PCI)
  – NPC
  – NSCLC
Morris et al. NEMJ Apr 15 1999 pp 1137 - 1143

SURVIVAL

Disease Free

Figure 1. Kaplan-Meier Estimates of Survival among Patients

Figure 2. Kaplan-Meier Estimates of Disease-free Survival among Patients Assigned to Receive Radiotherapy and Concur
CONCERNS WITH CONCURRENT CHEMO-RADIOThERAPY

- **Toxicity**
  - acute
  - *late especially bowel & bladder*
- **Dose of radiotherapy**
  - Maintain or need to reduce
- **Prolongation of treatment time**
  - detrimental in cervical squamous cancers
Drug Radiation interaction

Criticism

- Inadequate dose of radiotherapy
  - higher doses recommended currently
- Short follow-up
  - late toxicity
  - longer follow-up needed
- Prolonged treatment time
ANGIOGENESIS

- Establishment of a capillary network from the surrounding host tissue

ANGIOGENESIS (2)

- Tumours > 0.2 mm have necrotic centre
  - Tumours < 0.16 mm have no necrosis
  - Tumours consists of oxic and anoxic cell along a gradient of oxygen tension
- Chronic hypoxia
- Intermittent hypoxia
HYPOXIA & RADIO-RESISTANCE

- Low LET radiation cause indirect DNA damage by reactive radicals
  - Presence of oxygen is required.
  - Oxygen "fixation" (peroxidation) of molecular damage
- Anoxic cell up to 3x more radioresistant
  - Oxygen enhancement ratio (OER)
HYPOXIA AND CHEMO-RESISTANCE (?)

• Less established

• Possibly
  – Poor drug delivery
  – Lower proportion of cycling cells
    – Many chemo agents are cycle specific

• Molecular mechanism?
  – Early stress-response proteins
  – Modulation of cell cycle progression
  – Induction of chemo-resistant genes eg p-53
REDUCING HYPOXIA

• Modalities
  - Blood transfusions
  - Hyperbaric oxygen
  - Oxygen / carbogen breathing
  - Hypoxic cell radio-sensitizers
  - May improve radiotherapy results by 5%
TARGETING HYPOXIC CELLS

- Adding Oxygen
- Radiosensitizers
- Bioreductive agents
Hypoxic Cell Sensitizers

- Agents that mimic O2 and enhance radiation damage
- Efficiency of sensitization related to electron affinity of the agent
- Not rapidly metabolized by the cells
  - Should diffuse further than O2 to reach hypoxic cells
- Should be effective at relatively low RT doses as used in conventional fractionation
BIOREDUCTIVE DRUGS

- Compounds which have selective cytotoxicity towards hypoxic cells
- Drugs are metabolically reduced intracellularly in O2-deficient tissues to form cytotoxic compounds
- Activation of bioreductive drugs need hypoxia and endogeneous reductase
  - Xanthine oxidase, aldehyde dehydrogenase etc
- 1 e$^-$ or 2 e$^-$ transfer reductases
  \[
  \text{drug} + \text{enzyme} + e^- \rightarrow (\text{drug})^{--} \\
  \]
- In presence of oxygen, the drug is oxidised to original form
  \[
  (\text{drug})^{--} + \text{O2} \rightarrow \text{drug} + \text{O2}^{--} \\
  \]
Utility of Hypoxic cell cytotoxin
BIOREDUCTIVE AGENTS

- Classes
  - Nitro-imidazoles
  - N-Oxides
  - Quinones
    - aliphatic and heteroaromatic N-oxides.

- Unlikely to be active as single agent
- Combination with
  - Radiation
  - chemotherapy
Nitro-imidazoles

- Mimics oxygen effect - Fixes radiation damage similar to oxygen
  - Metronidazole
  - Misonidazole
  - Nimorazole
- Lead drug is Metronidazole
  - Others have side-chain modification
- also useful as markers of hypoxia (radiolabelled)
Proportion of rat mammary tumours controlled with single fraction of x-ray with and without misonidazole
Radiosensitization of Misonidazole

- Line 1 shows cell survival in oxic condition and Line 2 in nitrogen ie hypoxic.
- Adding misonidazole (Ro-0700582) appear to sensitize hypoxic cells to the radiosensitivity level of oxic cells
  - Increasing doses of misonidazole increases radiosensitivity of hypoxic cells.
Misonidazole – cervical cancer

Fig. 1. Absolute survival: radiotherapy alone compared to radiotherapy plus misonidazole.
Drug Radiation interaction

Nitroimidazole

- **Metronidazole**
  - more active
  - toxic
  - benefit in subgroups

- **Misonidazole**
  - less toxic
  - no benefit

- **Etanidazole**
  - less active
  - much less toxic
  - benefit in H&N Ca

- **Nimorazole**
<table>
<thead>
<tr>
<th></th>
<th>First-Generation Metronidazole</th>
<th>Second-Generation Misonidazole</th>
<th>Third-Generation Etanidazole</th>
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</thead>
<tbody>
<tr>
<td><strong>MTD</strong></td>
<td>Total cumulative dose not to exceed 54 g/m²&lt;br&gt;Multiple doses 6 g/m² three times a wk for 3-4 weeks</td>
<td>Total cumulative dose not to exceed 12 g/m²&lt;br&gt;Once or twice a week for 5-6 weeks</td>
<td>Total dose not to exceed 40.8 g/m² at 1.7-2 g/m² three times a week for 6 weeks&lt;br&gt;Single dose 12 g/m² during IORT&lt;br&gt;48 hours continuous infusion 20-21 g/m² during brachytherapy</td>
</tr>
<tr>
<td><strong>Optimal time for administration</strong></td>
<td>4 hours prior to radiation</td>
<td>4 hours prior to radiation</td>
<td>30 min prior to radiation</td>
</tr>
<tr>
<td><strong>Main toxicities</strong></td>
<td>Gastrointestinal toxicity +4&lt;br&gt;Sensory peripheral neuropathy +1</td>
<td>Sensory peripheral neuropathy +4&lt;br&gt;Gastrointestinal toxicity +2</td>
<td>Sensory peripheral neuropathy +3&lt;br&gt;Gastrointestinal toxicity +1&lt;br&gt;Arthralgia +1, seen more often with 48 hours continuous infusion</td>
</tr>
<tr>
<td><strong>SER</strong></td>
<td>Estimated SER 1.15 with multiple doses of 6 g/m²</td>
<td>Estimated SER 1.4 with multiple doses of 2 g/m²&lt;br&gt;Estimated SER 1.15 with doses of 0.5 mg/m²</td>
<td>Estimated SER 1.6 with multiple doses of 1.7-2 g/m²&lt;br&gt;Estimated SER 2.5-3.0 with doses of 12 g/m²</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>Not currently in use as a radiosensitizer[^7],[^8]</td>
<td>No longer in use as a first line radiosensitizer[^9],[^12]</td>
<td>No longer in use as a first line radiosensitizer[^14-17]</td>
</tr>
</tbody>
</table>
QUINONES

• **Mitomycin C**
  - From *Streptomyces caesporiosus*
  - Activated by reductase
    - Esp. NADPH-dependant mitochondrial reductase
  - Produces semiquinone radical anion that covalently interacts with DNA causing cross-links lesions
  - Less selective towards hypoxic cells

• **Porfiromycin**
  - Analogue of MMC
  - 10-fold oxic / hypoxic differential
Nitro-aromatics (N-OXIDES)

- **Tirapazamine**
  - Reduced by C P-450 to nitrooxide radical
    - Reacts with DNA to produce single / double strand breaks
  - Differential 30 – 300x in cell lines
  - Increasing cytotoxicity as oxygen levels are diminished
- Side-effects
  - Nausea, vomiting, diarrhoea and skin rash
Tirapazamine in NSCLC – CATAPULT trial

In a randomised trial of concurrent chemo-radiation, addition of tirapazamine to cisplatin improved the survival of patients.

NSCLC – Tirapazamine plus Taxol Carbo

No improvement was seen in another trial using paclitaxel-carboplatin combination

Fig 2. Overall survival. Carbo, carboplatin.
Why the discrepancies?

Nimorazole vs placebo
- Osteopontin levels

\[ \text{Low} \]
\[ \text{Intermediate} \]
\[ \text{High} \]

- We just do not know enough!!
- Many other variables in hypoxia
  - Osteopontin
  - HIF1
  - Unfolded protein response etc
- Graphs show that the effect of nimorazolate is only seen in tumours with high osteopontin

RADIATION PROTECTORS
PROTECTION OF NORMAL TISSUE

- Apart from increasing the sensitivity of tumours to radiation by using radiosensitizers, another approach would be to protect normal tissue by radiation protectors.
- Radiation protector should selectively protect normal tissues without protecting tumours.
- The graph for complication rate moves to the right while the tumour control rate remains the same (next slide).
- As radiation protectors not specific, drug delivery to normal tissue should be enhanced.
PROTECTION OF NORMAL TISSUE

With addition of radiation protector, graph moves to right

Tumour control remains the same
Characteristics of an ideal radiation protector

- Acts selectively in normal tissue compared to tumour, preferably excluded from tumour
- Reaches normal tissue in adequate concentration
- Predictable pharmacokinetics for timing with radiation therapy
- Able to be administered with every radiation treatment in a standard regimen
- Minimal toxicity of the drug itself
- Results in reduced acute or late effects
Potential mechanisms of action

Prevents DNA damage
- Alters cell biochemical and molecular response to radiation
- Enhances repair of radiation damage
- Enhances repopulation of normal tissue
- Alters late effect

Mechanisms at chemical level:
- Free radical scavenging – protects against O2-based free radicals generated by radiation (or chemo. eg alkylating agents)
- Hydrogen atom donation – to facilitate direct chemical repair at sites of DNA damage
Dose Reduction Factor

- True radioprotectors modify the radiation effects:

  **Dose-reduction factor (DRF)**

  
  \[
  \text{DRF} = \frac{\text{radiation dose with protector}}{\text{radiation dose without protector}}
  \]

  for the same level of effect

- **Sulphhydryl compounds:** SH—CH$_2$—…CH$_2$—NH$_2$
  - Scavenges (mops up) free radicals by its free SH group (thiol)
  - Efficient radioprotectors against sparsely-ionizing radiations (low LET)
  - eg. cysteine, cysteamine, glutathione, amifostine
Radioprotectors in use

- Often researched by army for use in nuclear conflicts
- Cystaphos:
  - carried in field pack by Russian army KIV nuclear conflict
- Amifostine:
  - used in clinical radiotherapy and
  - carried by US astronauts on lunar trips
  - Not used by army due to side-effects
Amifostine

- Ethyl®, WR2721
- Approved by US FDA for clinical use:
  - Radiotherapy:
    - To reduce post-radiation xerostomia for Head&Neck Ca where radiation port includes a substantial portion of the parotid glands
  - Chemotherapy:
    - To reduce cumulative renal toxicity associated with repeated administration of cisplatin in advanced Ovarian Ca and Lung Ca
- RTOG Ph III trial for H&N Ca: amifostine delivered daily, 30 mins before RT → lower incidence of xerostomia, better QOL, no deterioration in locoregional tumour control (but is always a worry!)
Amifostine

- Is a phosphorothioate:
  - non-reactive, does not readily permeate cells
- Pro-drug
  - Metabolised to active metabolite WR-1065 by: alkaline phosphatase, a plasma membrane enzyme, the primary enzyme for dephosphorylation
  - Alkaline phosphatase is present in high concentration in normal tissues and capillaries
- WR-1065 readily enters normal cells by facilitated diffusion
Amifostine

- **Mechanisms of action proposed:**
  - Scavenging of free radicals
  - Hydrogen donation
  - Binding to critical biologic targets
  - Mixed disulfide formation

- **Toxicity:**
  - nausea, vomiting,
  - hypotension,
  - allergic reaction,
  - hypocalcemia

- **Precautions:** monitor blood pressure every 5 mins during amifostine infusion. Interrupt if blood pressure falls.
Differential effect of Amifostine in normal tissue versus tumours

• Actively transported into normal tissues by **facilitated diffusion**, but solid tumours absorb drug slowly by passive diffusion
  – Therefore increased concentration in normal tissue
• Reduced delivery of amifostine to tumour due to **deficient tumour vasculature**
  – Reduces drug available to tumours
• **Intracellular conversion** of amifostine is slower in tumours which have lower inherent levels of alkaline phosphatase and more acidic pH compared to normal tissues
  – Higher levels of activated drug in normal tissue

→ Need to give radiotherapy soon after amifostine (30 mins) to exploit the differential effect (from absorption and conversion)
  → If given several hours before radiation, tumours are able to accumulate and activate amifostine similar to normal tissues.
Other radioprotectors

- Under clinical trials: Nitroxides – tempol, proxyl
- Not true protectors but reduces normal tissue effects
  - Vasoconstrictors etc. → reduces O2 to cells etc
    - eg. pilocarpine (RTOG trials), epinephrine, histamine, serotonin, carbon monoxide etc.
- Cytokines eg. growth factors
  → to enhance repopulation of normal tissues ?modify radiation response
    - eg. Keratinocyte Growth Factor, EGF, TGF, Interleukin
**CONCLUSION**

- Addition of drug / chemotherapy to radiation may result in interactive or non-interactive action.
- Non-interactive processes can be demonstrated to have clinical benefits.
- Therapeutic gain is only achieved if interaction results in increased response relative to toxicity.
- Radiation sensitizer are used to increase sensitivity of hypoxic cells to radiation.
  - Sensitizer mimic oxygen effect to fix radiation damage.
- Bioreductive drugs are selectively toxic to hypoxic cells.
  - They are activated under hypoxic condition to active metabolites.