3/27/13 lecture

Radioprotectors

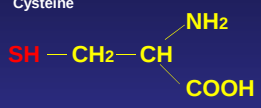
Tumor hypoxia and radiosensitizer

Chemotherapy agents

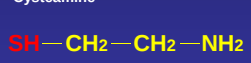
Radioprotectors

Discovery of radioprotector

Cysteine



Cysteamine



Dose Reduction Factor
DRF

$$\text{DRF} = \frac{\text{Dose of RT with the drug}}{\text{Dose of RT without the drug}}$$

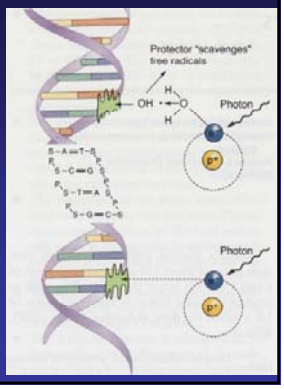
Structural features of radioprotectors

- A free SH group at one end
- A strong basic group at the other end (amine or guanidine)
- A straight chain of two or three carbon atoms to connect two ends

Mechanism of action

Free radical scavenger

Parallel oxygen effect
Maximal effect for sparsely ionizing radiation
Minimal effect for densely ionizing radiation
DRF equal OER with a value 2.5 to 3



Development of "more effective" compounds

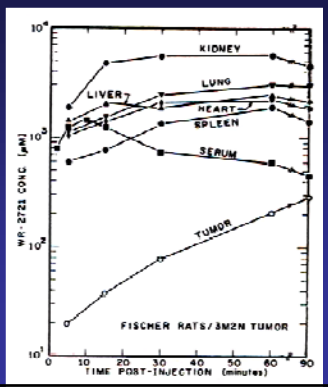
Table 11-2.
Three Protectors in Practical Use

COMPOUND	STRUCTURE	USE
WR-638	$NH_2CH_2CH_2SPO_3HNa$	Carried in field pack by Russian army (Cystaphos)
WR-2721	$NH_2(CH_2)_2NHCH_2CH_2SPO_3H_2$ amifostine	Protector in radiotherapy and carried by US astronauts on lunar trips (amifostine)
WR-1607	$CH_3(CH_2)_3NHCH_2CH_2SSO_3H$	Marketed as rat poison (d-CON)

Comparison of Hematopoietic and Gastrointestinal Dose Reduction Factors in Mice for the Three Compounds Listed Above

COMPOUND	DRUG DOSE (mg/kg)	DRF (7 DAYS)	DRF (30 DAYS)
WR-638	500	1.6	2.1
WR-2721	900	1.8	2.7
WR-1607	10	—	2.1

Amifostine as a radioprotector in RT



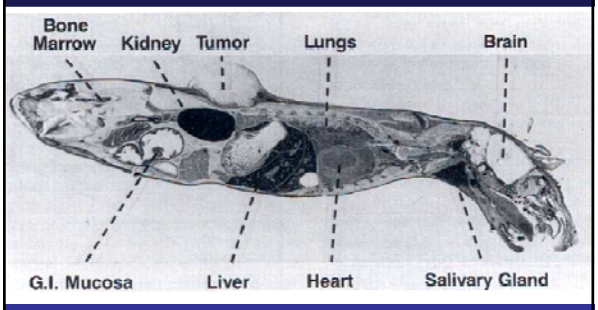


Table 11-3.
Summary of Normal Tissue Responsiveness to Protection by WR-2721

TISSUES PROTECTED*	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)	

Numbers in parentheses are the dose reduction factors or factor increases in resistance associated with WR-2721 injection. (From Yuhas JM, Spellman JM, Culo F: In Brady L [ed]: Radiation Sensitizers, pp 303–308. New York, Masson, 1980)

Phase I toxicity data

- Dose-limiting toxicity– hypotension
- Other toxicities include
  - Nausea/vomiting
  - Sneezing
  - Somnolence
  - Allergic reaction

First ever phase III randomized trial with amifostine

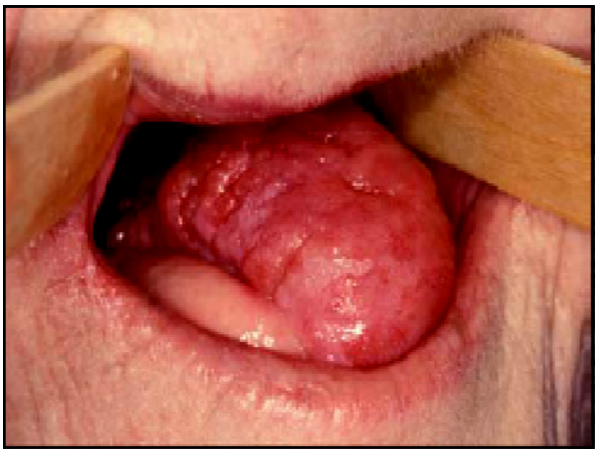
- 100 patients with unresectable or recurrent adenomacarcinoma of rectum
- RT ± amifostine
- Amifostine 15 minutes before RT 4 days a weeks for 5 weeks
- Protection of skin, mucous membrane, bladder and pelvix structures

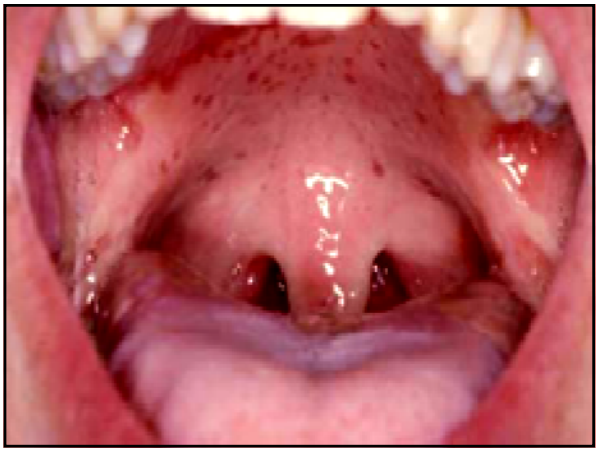
Kligerman MM et al. Int J Radiat Oncol Biol Phys 22:799-802, 1992

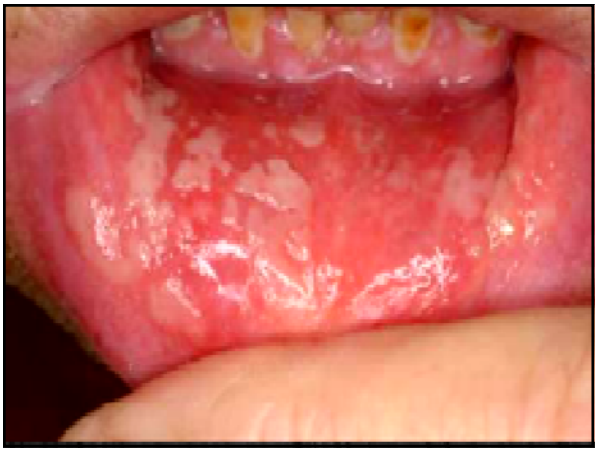
Radioprotector and chemotherapy

- Protection against nephrotoxicity, ototoxicity and neurotoxicity from CDDP
- Protection against hematologic toxicity from cyclophosphamide

Amifostine in the treatment of head and neck cancer







Fractionation: RTOG 90-03

Organ/Tissue	Grade	SFx (N=263)	HFx (N=263)	Afx-split (N=274)	Afx-CB (N=268)
Mucous membrane	1	33(12)	27(10)	25(9)	30(11)
	2	146(56)	111(42)	118(43)	104(39)
	3	67(25)	109(41)	109(40)	122(46)
	4	0(0)	1(1)	3(1)	1(1)
Salivary gland	1	57(21)	60(23)	60(22)	50(19)
	2	175(67)	170(64)	174(64)	155(72)

IJROBP 48(1):7, 2000

IMRT vs Standard RT

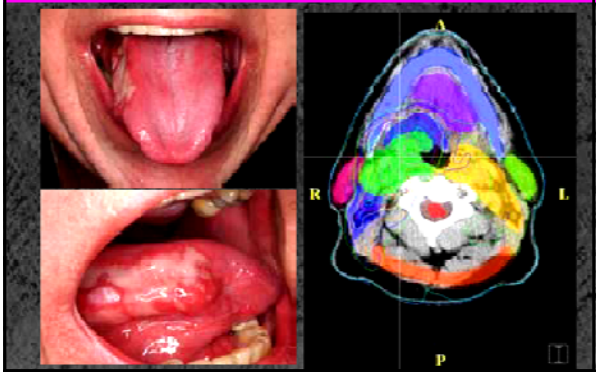
Standard RT	IMRT
3-field lateral beams with entry and exit	Multiple beam angles

- Due to multiple beam angles, mucositis may arise in unexpected locations

IMRT = intensity-modulated radiation therapy
RT = radiation therapy

R Tonsil Cancer T1N1M0 66Gy/30fx

Isodose Distribution Magenta-70 Red-68 Yellow-66 Orange-62 Blue-60 Green-56



Phase III Trial of RT Toxicity

Amifostine Amelioration: Design

STRATIFY

- Treatment center
- Tumor site
- Definitive vs postoperative adjunctive RT
- Node positive vs negative
- Karnofsky Performance status

RANDOMIZE

- Arm I (n = 150): Amifostine: 200 mg/m² IV; RT: 1.8 to 2.0 Gy/d; Total: 50 to 70
- Arm II (n = 152): RT alone; RT alone: 1.8 to 2.0 Gy/d; Total: 50 to 70

Entry criteria:

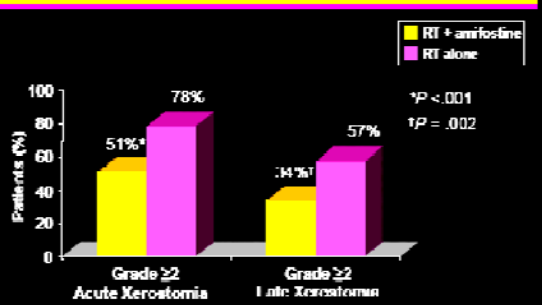
- ≥75% of both parotid glands within radiation fields to doses ≥40 Gy
- KPS ≥60

IV = Intravenous
KPS = Karnofsky Performance status
RT = radiation therapy

Brizel DM et al. J Clin Oncol. 2000;18:3339-3345.

Phase III Trial of RT Toxicity

Amifostine Amelioration: Results



RT = radiation therapy

Adapted from Brizel DM et al. J Clin Oncol. 2000;18:3339-3345.

Phase II Study of Head and Neck Cancer

Prophylaxis of Radiochemotherapy-Induced Morbidity

50 patients (45 evaluable) T2N0M0 head and neck cancer

RANDOMIZE

- Arm 1* (n = 22): Amifostine 300 mg/m² IV
- Arm 2 (n = 23): Control (no amifostine)

45 patients: RT total dose 50 to 74 Gy + carboplatin 30 mg/m²

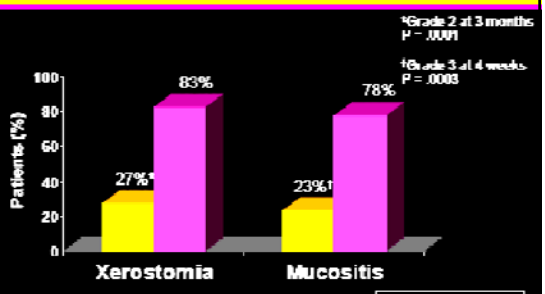
*protocols in amendment prompted revision of schedules, agendas, and premedication prior to amifostine therapy.

IV = Intravenous
RT = radiation therapy

Antoniades D et al. Int J Radiat Oncol Biol Phys. 2003;57:739-747.

Phase II Study of Head and Neck Cancer

Reduction of Xerostomia and Mucositis

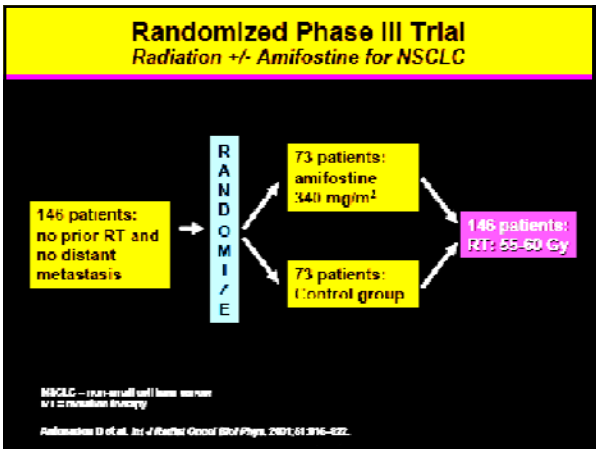


RCT = radiochemotherapy

Antoniades D et al. Int J Radiat Oncol Biol Phys. 2003;57:739-747.

Amifostine in the treatment of lung cancer

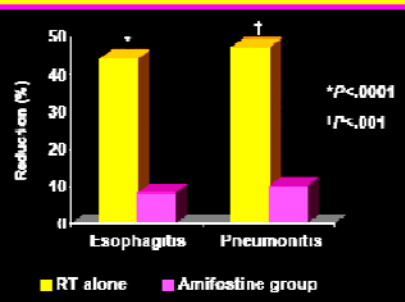
Randomized Phase III Trial
Radiation +/- Amifostine for NSCLC



NSCLC = non-small cell lung cancer
RT = radiation therapy

Antonadou D et al. Int J Radiat Oncol Biol Phys. 2001;51:916-922.

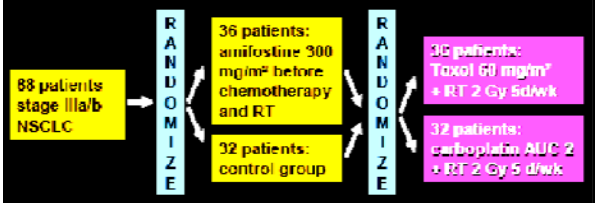
Randomized Phase III Trial
Radiation +/- Amifostine for NSCLC



NSCLC = non-small cell lung cancer
RT = radiation therapy

Antonadou D et al. Int J Radiat Oncol Biol Phys. 2001;51:916-922.

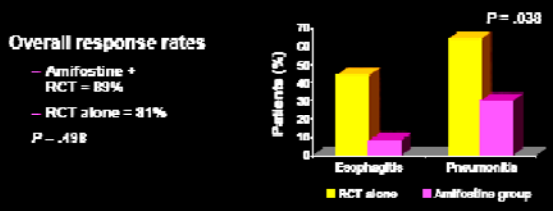
Randomized Phase II Trial
Chemotherapy +/- Amifostine in Stage IIIA/B NSCLC



AUC = area under the curve
NSCLC = non-small cell lung cancer
RT = radiation therapy

Antonadou D et al. ASCO 2004. Abstract.

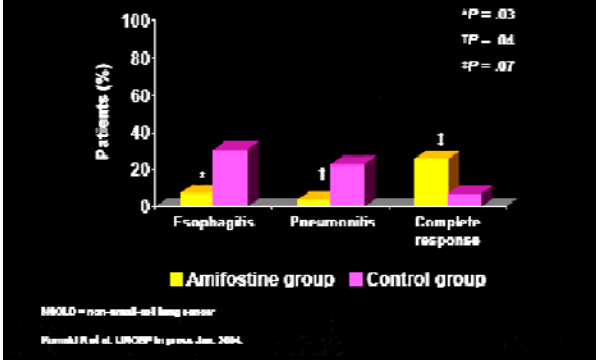
Outcomes
Esophagitis and Pneumonitis



RCT = radiochemotherapy

Antonadou, et al. Proc Am Soc Clin Oncology. 2000;19:[illegible].

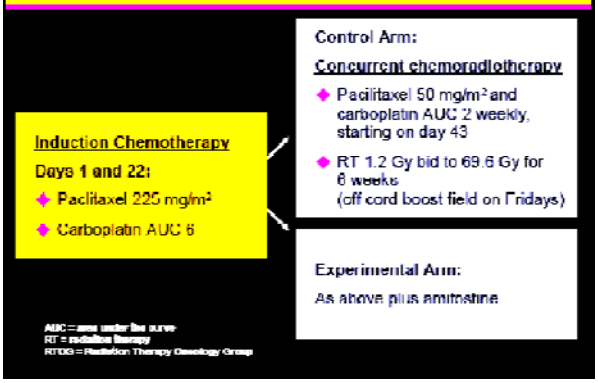
Randomized Phase III Trial
Amifostine With Concurrent Chemotherapy and Hyperfractionated Radiation Therapy for Inoperable NSCLC



NSCLC = non-small cell lung cancer

Komaki R et al. LBCRP In press Jan. 2004.

RTOG 98-01: Schema



AUC = area under the curve
RT = radiation therapy
RTOG = Radiation Therapy Oncology Group

Amifostine Dose and Schedule

- Dose: 500 mg IV over 5 min
- Timing:
  - *15-60 min before RT on "RT only" days
  - *90-180 min before RT on "chemo-RT" day (treatment order: amifostine-chemo-RT)
- Schedule: Monday-Thursday, before PM fraction of RT (first 15 patients received amifostine before AM RT fraction)

IV = intravenous
RT = radiation therapy

Late Esophagitis

3 Grade 3 in the amifostine arm

vs

2 Grade 3 in the control arm ($P = 0.6$)

Average Area Under the Curve: Physician vs Patient Assessment

	Amifostine	No Amifostine	*P* value
CTC grade (at least 3 physician assessments) n = 102; 98	1.06 (0-2.7)	1.1 (0-2.4)	0.323
Swallowing score (at least 15 patient assessments) n = 96; 96	2.19 (1-3.76)	2.34 (1-3.5)	0.025

CTC = common toxicity criteria

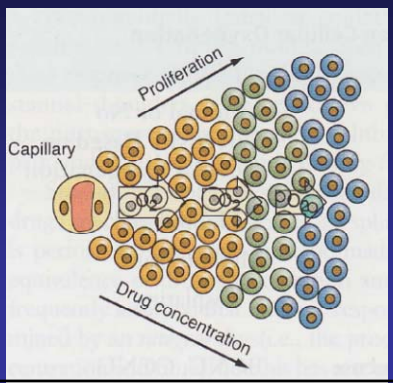
Conclusions

- Amifostine did not reduce severe esophagitis in patients with lung cancer receiving concurrent chemotherapy and hyperfractionated RT in the dose and schedule given.
- However, based on patient swallowing diaries, area under the curve of esophagitis was significantly lower with amifostine.

RT = radiation therapy

Tumor hypoxia and radiosensitizer

Oxygen diffusion from a capillary



Overcoming hypoxia

- **Increase oxygen supply**
  - Hyperbaric oxygene, carbogen
  - Blood transfusion
  - Stop smoking
- **High-LET radiations, neutrons, heavy ions**
- **Chemical radiosensitizers**
- **Hypoxic cytoxins**

Hypoxic cell radiosensitizers

- Selectively sensitize hypoxic cells
- Chemically stable
- Highly soluble and able to diffuse some distance (200 um)
- Be effective at therapeutic RT dose range

Nitroimidazoles

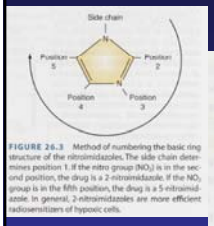
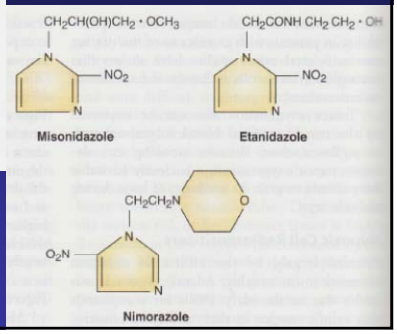
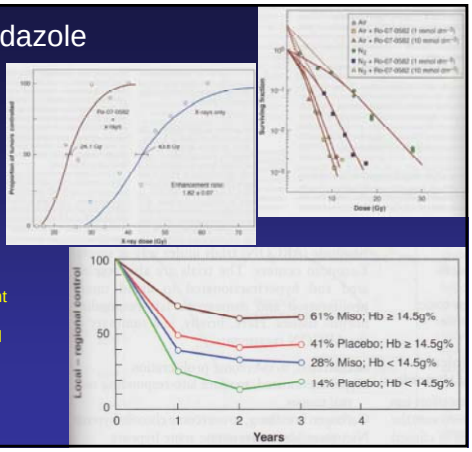


FIGURE 26.3 Method of numbering the basic ring structure of the nitroimidazoles. The side chain determines position 1. If the nitro group (NO_2) is in the second position, the drug is a 2-nitroimidazole. If the NO_2 group is in the fifth position, the drug is a 5-nitroimidazole. In general, 2-nitroimidazoles are more efficient radiosensitizers of hypoxic cells.



Misonidazole

- Produced appreciable sensitization with cells in culture
- Also had a dramatic effect in animal studies
- Enhancement ratio of 1.8 was obtained
- In clinical trials, no benefit observed



Etanidazole & Nimorazole

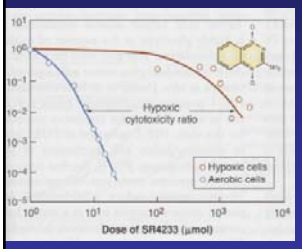
- Etanidazole is less toxic than misonidazole
- Higher dose could be given
- No benefit in clinical trials

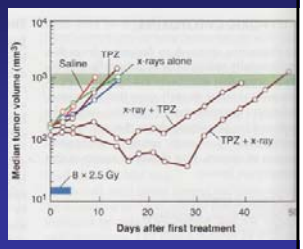
- Nimorazole is much less toxic, and less effective
- Very high dose can be given
- In a Danish trial it produced a significant improvement in local control and survival compared with RT alone in patients with supraglottic and pharyngeal cancer, but no further studies have been done since

Hypoxic cytoxins

selectively kill hypoxic cells

- Tirapazamine showed highly selective toxicity toward hypoxic cells both in vitro and in vivo, but again, no significant benefit was seen in human clinical trials.





Chemotherapy agents

Classes of chemotherapy agents

- Alkylating agents
- Antibiotics
- Antimetabolite
- Nucleoside analogues
- Vinca Alkaloids
- Others not belong to the above
- Topoisomerase inhibitors
- Targeted agents

Alkylating agents

- Highly reactive, substitute alkyl groups for hydrogen atoms of DNA
  - Nitrogen mustard derivatives
  - Ethylenimine derivatives
  - Alkyl sulfonates
  - Triazine derivatives
  - nitrosoureas
- Cell cyclic non-specific

Antibiotics

- Directly bind to DNA, inhibit DNA and RNA synthesis
  - Doxorubicin
  - Daunorubicin
  - Dactinomycin
  - Bleomycin
  - Mitomycin
- Cell cycle non-specific

Antimetabolites

- Analogues of normal metabolites
  - Methotrexate
  - 5-Flurouracil
- Action mechanisms
  - Substituting for a metabolite
  - Competing with normal metabolite to either occupy catalytic site of a key enzyme or at an enzyme regulatory site

Nucleoside analogues

- Cytarabine – analogue of deoxycytidine
  - Competitive inhibitor of DNA polymerase
- 5-Azacytidine – analogue of cytidine
  - Inhibit process of large molecular weight RNA

Vinca Alkloids

- From plants
- Bind to cellular microtubular proteins inhibiting microtubule polymerization
- Vincristine

Taxanes

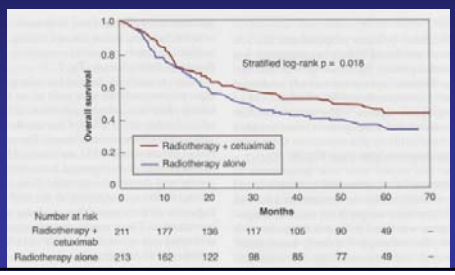
- Microtubule-stablizing agents
- Block or prolong the transit time of cells in the G2/M phase of cell cycle
- Paclitaxel is the prototype
- Docetaxel is largely synthetic

Others

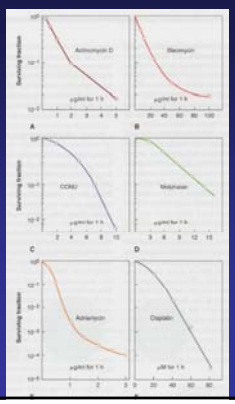
- Procarbazine
  - Precise action mechanism not clear
- Hydroxyurea
  - Inhibitor of ribonucleotide reductase
  - Specifically toxic to cells in S-phase
  - Cause piling up at a block at G1/S interface
- Cis-platinum
  - Causing both inter and intrastrand crosslinking
  - Inhibit DNA synthesis
  - Cell cycle non-specific
  - May be more toxic to hypoxic cells

Targeted agents

- Cetuximab
- bevacizumab



Dose-response relationship



Sublethal and potentially lethal damage repair

- Sublethal damage repair
  - Survival increases if a dose is divided into two or more small doses separated in time
- Potentially lethal damage repair
  - Increase in survival if cells held in non-proliferative state for some time after treatment

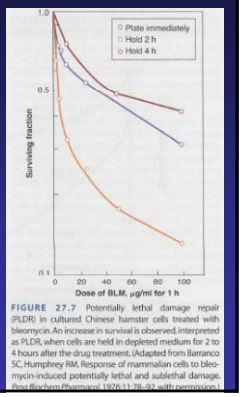


FIGURE 27.7 Potentially lethal damage repair (PLDR) in cultured Chinese hamster cells treated with bleomycin. An increase in survival is observed, interpreted as PLDR, when cells are held in depleted medium for 2 to 4 hours after the drug treatment. (Adapted from Barranco SC, Humphrey RM. Response of mammalian cells to bleomycin-induced potentially lethal and sublethal damage. Proc Biochem Pharmacol 1976;11:78–92 with permission.)

The oxygen effect

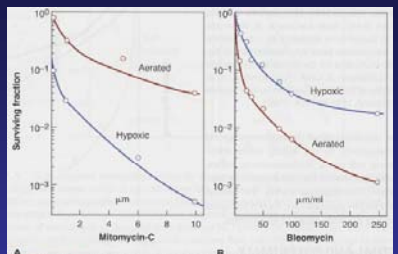


FIGURE 27.8 Molecular oxygen can be either a sensitizer or a protector, depending on the particular chemotherapeutic agent. **A:** Survival curves for EMT6 cells treated for 1 hour with graded doses of mitomycin C under aerated or hypoxic conditions. In the absence of oxygen, the cells are substantially more sensitive. (Data from Teicher BA, Lazo JS, Sartorelli AC. Classification of antineoplastic agents by their selective toxicities toward oxygenated and hypoxic tumor cells. *Cancer Res.* 1981;41:73–81.) **B:** Survival curves for Chinese hamster cells in culture exposed for 4 hours to graded doses of bleomycin under aerated or hypoxic conditions. In the absence of molecular oxygen, the cells are more resistant. (Adapted from Roizin-Towle L, Hall EJ. Studies with bleomycin and misonidazole on aerated and hypoxic cells. *Br J Cancer.* 1978;37:254–261 with permission.)

Resistance to chemotherapy and hypoxic cytoxins

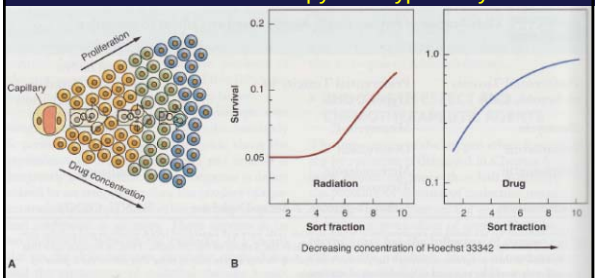


FIGURE 27.9 Illustrating why the microenvironment in a tumor may lead to resistance to chemotherapy agents. **A:** Oxygen diffuses from a capillary, but the concentration falls with distance because of respiration in the mass of tumor cells. This leads to a region of hypoxia and a region of anoxia. Chemotherapeutic agents must also diffuse through a tumor from capillaries. The effect of the agent decreases with distance from the capillary because the drug concentration falls because of metabolism, proliferation decreases with distance from a capillary because of lack of oxygen, and cells that are not dividing are resistant to many chemotherapeutic agents. **B:** The fraction of cells surviving a treatment with radiation or most chemotherapeutic agents rises with distance from a capillary because both are less effective in hypoxic nondividing cells. (Adapted in part from Brown JM, Siim BG. Hypoxia-specific cytotoxins in cancer therapy. *Semin Radiat Oncol.* 1996;6:22–36, with permission.)

Drug resistance

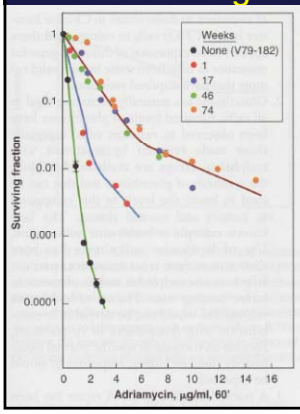


FIGURE 27.10 Change in survival response to doxorubicin (Adriamycin) of Chinese hamster cells grown in culture and exposed continuously to a low concentration of the drug (0.05 μg/ml) for prolonged periods, namely, 1, 17, 46, or 74 weeks. The closed circles show the survival response for the parent cell line. A dramatic resistance to the drug develops by 17 weeks; that is, prolonged exposure at a low concentration renders the cells resistant to subsequent high concentrations. (Adapted from Belli JA. Radiation response and Adriamycin resistance in mammalian cells in culture. *Front Radiat Ther Oncol.* 1979;13:9–20, with permission.)

Drug resistance

- Resistance to chemotherapy agents is acquired quickly, uniformly and inevitably
- Gene mutation, stem cells and ANC transporter
- Use a battery of different drugs to overcome resistance
- Pleiotropic resistance
  - The development of resistance to one drug results in cross-resistance to other drugs, even those with different mechanisms of action
- Resiatnce to chemotherapy does not mean resistance to radiation.

Combination of chemotherapy and radiation therapy

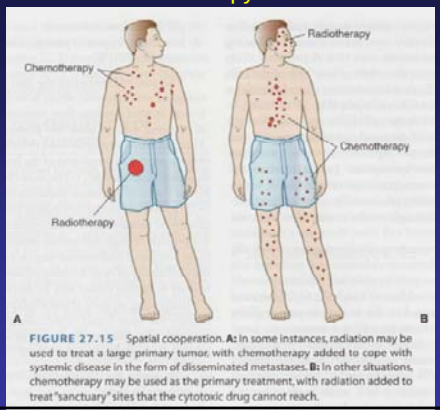


FIGURE 27.15 Spatial cooperation. **A:** In some instances, radiation may be used to treat a large primary tumor, with chemotherapy added to cope with systemic disease in the form of disseminated metastases. **B:** In other situations, chemotherapy may be used as the primary treatment, with radiation added to treat "sanctuary" sites that the cytotoxic drug cannot reach.

Combination of chemotherapy and radiation therap

- Induction chemotherapy
- Concurrent chemotherapy
- Adjuvant chemotherapy

Assays for sensitivity of individual tumors

- Biopsy specimens
- In vitro
- Xenografts in animals

Cytoxic drugs can also induce second malignancies

- The greatest relative risk is leukemia
- The greatest in number is solid tumors