Chemoradiation Interactions and Toxicity Management

Jonathan W. Thompson
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University of Alabama At Birmingham, Department of Radiation Oncology
Radiation Oncology Associates of Acadiana, Lafayette, LA
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Objectives:

• General overview of the biology of cancer therapies
• Mechanisms of action of chemotherapy and radiation therapy
• Explore the different chemotherapy classes and common agents
  – Emphasis on those used with radiation
• Understand radiation synergy and special cases of toxicity
• Management of common toxicities
Many anti-tumor functions of chemotherapy are similar to those caused by radiation
Affect DNA synthesis or function
Most preferentially target proliferating cells
In general, radiation sensitivity and chemotherapy sensitivity are in parallel
Radiation Biology
Radiation-Induced Cell Killing

• Radiation therapy induces ionization within cells
  – Killing occurs as a direct result or via free radical formation
• DNA is the target
  – Ionization and free radicals induce single strand breaks (SSBs) and double strand breaks (DSBs)
• Repair of SSBs and DSBs can occur
Radiosensitivity

• Preferential radiosensitivity is exhibited
  – Different phases of cell cycles
  – Architecture/molecular biology
  – This is for standard, fractionated therapy

• Some conditions enhance cellular killing
  – Increased oxygen concentrations
  – Synergistic chemotherapies
Cell Cycle
Radiosensitivity

• Most radioresistant: S phase
  – Chromosomes are duplicated and sister chromatid is available as a template

• Most radiosensitive: G2 and M phases
  – DNA is unwound and is separating
  – Template strand is less available as a repair template

• Some cell types are more radiosensitive than others
Chemotherapy Biology
Broad Classification of Cytotoxic Therapy

• Cell-cycle Specific: agents mainly effective during certain times of the cell-cycle
  – Paclitaxel affects microtubules and blocks cells at the G2/M checkpoint
  – Cisplatin causes interlinking of DNA and is manifested in the S-phase

• Cell-cycle non-specific: action is independent of cell cycle
Oxygen Effects

• Different agents show varied dependence to oxygen concentrations
  – Aerobic preference: bleomycin, procarbazine, dactinomycin
  – Hypoxic preference: MMC, Adriamycin
  – No preference: 5-FU, MTX, CDDP, CCNU

• These differences are often exploited in clinical situations
Chemotherapy Resistance

• Multidrug resistance by drug extrusion via cellular membrane proteins
• Increased glutathione concentrations in resistant cells
  – Free radical scavenger
• Marked increase in DNA repair processes
• Chemotherapy resistance does not seem to crossover into radiation resistance
“Spatial Cooperation”

• One of the first theories of chemotherapy and radiation interaction

• Radiation is more effective at controlling local tumors
  – Only treats what it “sees”
  – Surgery fits here, as well

• Chemotherapy can handle micrometastases
  – Cannot handle bulky primary sites or “sanctuary” sites of disease
Chemoradiation Synergy

• We now know that chemotherapy and radiation therapy can help each other. . .
  – Chemotherapy augments local control
  – Radiation therapy can even induce control of distant disease in some scenarios
Example of Synergy
Outline of How Synergy Occurs:

• Drug causes accumulation at G₂/M
  – Radiosensitive phase of the cell cycle
• These cells are more likely to be killed by XRT
  – Overall tumor burden is decreased
• Process repeats itself, each time with a decreasing cell burden and higher likelihood of overall tumor control
Common Chemotherapeutics
Select Alkylators

• Nitrogen Mustards:
  – Cyclophosphamide (Cytoxan), Ifosfamide (Ifex)

• Triazine derivative:
  – Temozolamide (Temodar)

• Nitrosureas:
  – BCNU (carmustine)
  – CCNU (lomustine)

• Platinums have a similar MOA, discussed separately
Temozolamide (Temodar)

• Used most commonly in primary gliomas
• Hypermethylation of the MGMT promoter region causes epigenetic silencing of the AGT protein
  – Non-methylated tumors have enhanced repair of the DNA damage, diminishing response

Hegi et al. NEJM 2005
Temozolamide (Temodar)

• Felt to be synergistic with radiation therapy due to increasing the number of XRT-induced DSBs

• Toxicities:
  – Nausea and vomiting
  – Myelosuppression (especially thrombocytopenias)
    • Hold at PLTs of < 80K-100K

Chakravarti et al. CCR 2006
Antibiotics

- Produced from various strains of *Streptomyces* fungus
- Directly bind to DNA to produce effects thereby effecting RNA and protein
  - Cell cycle non-specific
- Examples:
  - Adriamycin*
  - Dactinomycin
  - Bleomycin
  - Mitomycin C*
Adriamycin (Doxorubicin)

- Directly intercalates in DNA chains
  - Inhibits topoisomerase II, blocks replication, and may form free radicals
- Commonly used in breast cancer, lymphoma, and sarcoma
Adriamycin (Doxorubicin)

• Radiation recall
  – Most commonly described in the setting of antibiotic-type agents, other chemo has been implicated
  – Proposed mechanisms: vascular changes, DNA repair deficiencies in irradiated cells, absence of stem cells in field, increased drug sensitivity
  – Most commonly occurs with separation of treatment modalities of < 2 months

Hird et al.  Current Oncology 2008
Adriamycin (Doxorubicin)

• Toxicities:
  – Myelosuppression
  – Cardiotoxicity, synergistic with Herceptin and possibly radiation
    • Maximum lifetime dose of 400-500 mg/m²
  – Avoid concurrent radiation therapy whenever possible

Hird et al.  Current Oncology 2008
Mitomycin-C

- In vivo activation to an alkylating agent with increased toxicity in hypoxic cells
- Most clinically useful in anal cancer
- Synergistic with radiation therapy
- Toxicity:
  - myelosuppression
Antimetabolites

• Analogues of normal metabolites required for cellular function

• Modes of action:
  – Substituting into a key cellular molecule
  – Competing for a catalytic site on an enzyme
  – Competing for a regulatory site on an enzyme

• Examples:
  – Methotrexate
  – 5-FU and Capecitabine (Xeloda)
  – Gemcitabine (Gemzar)
Methotrexate

- One of the first useful chemotherapies
  - Read "The Emperor of All Maladies"
- Competitively inhibits dihydrofolate reductase with affinity 1000x that of folic acid
  - Cell cycle dependent
- Halts DNA synthesis as a result
Methotrexate

• Too many uses to name.
• Mild synergy with radiation
• Toxicities:
  – Myelosuppression
  – Rare encephalopathy when given concurrently with brain XRT, risk lessened if given prior to XRT
  – Becomes important with sequencing of therapy
5-FU, Capecitabine (Xeloda)

- Xeloda is a prodrug of 5-FU
- 5-FU is a thymidilate synthase inhibitor thereby blocking thymine synthesis and causing downstream effects
5-FU, Capecitabine (Xeloda)

• Wide range of uses: head and neck cancer, GI malignancy, breast cancer

• Toxicities:
  – Myelosuppression
  – Hand-foot syndrome
  – Neurotoxicity

• These side effects are amplified in DPD deficiency
Hand-Foot Syndrome

• Palmar-plantar erythrodysesthesia
• Redness, swelling, and pain in the palms of the hands and the soles of the feet
  – Occasional blistering
• Many drugs implicated
• Prevention: mainly friction avoidance
• Treatment: topical corticosteroids, NSAIDs, topical lidocaine
Dihydropyrimidine dehydrogenase (DPD) deficiency

• About 80% of administered 5-FU is immediately broken down in the liver by DPD

• Individuals can be heterozygous or homozygous for the loss of the enzyme
  – Only about 0.2% homozygous in the population

• Heterozygotes can still have severe and fatal reactions owing to 5-FU toxicity
Gemcitabine (Gemzar)

- Used in pancreatic, bladder, and occasionally metastatic lung cancer
- Mechanism slightly different and involves S-phase specific DNA synthesis inhibition
- Strongly synergistic with radiation therapy
  - Very limited fields may be okay
- Toxicities:
  - Myelosuppression
Vinca Alkaloids

- Produced from plants (periwinkle)
- Work by inhibiting cellular microtubule formation (tubulin) and polymerization leading to mitotic arrest
  - Cell cycle specific at G₂
- Examples:
  - Vincristine (Oncovin)*
  - Vinblastine (Velban)
  - Vinorelbine (Navelbine)*
Vincristine (Oncovin)

- Used primarily in CNS malignancies, lymphoma (MOPP, CHOP)
- Felt to have some synergy with radiation therapy
- Toxicities:
  - Neurotoxicity in the form of peripheral neuropathies
Taxanes

- Produced from the yew tree
- Potent microtubule stabilizers and promoters of microtubule assembly thereby blocking or prolonging the G₂/M phase
  - Unable to form competent spindle assembly
- Examples:
  - Paclitaxel (Taxol)
  - Docetaxel (Taxotere)
Vinca alkaloids prevent microtubule assembly.

Alpha tubulin

Beta tubulin

Taxanes prevent microtubule disassembly.
Paclitaxel (Taxol)

- Many uses: lung, GYN malignancies, breast
- Some synergy with radiation therapy
- Toxicities:
  - Myelosuppression
  - Mucositis
  - Peripheral neuropathy
  - Hypersensitivity (requires pre-medication)
Topoisomerase Inhibitors

- Topoisomerases are responsible for maintaining DNA structure (loosening twisting and coiling)
- Topo I inhibitors: prevent resealing of DNA breaks in actively replicating cells
- Topo II inhibitors: prevent DNA re-ligation
- Examples:
  - Etoposide (Vespid, VP-16)
  - Irinotecan (Camptosar)
Etoposide (Vespid)

- Many uses: GCTs, lung, high-dose therapy in preparation for BMT
- Some synergy with radiation
- Toxicities:
  - Myelosuppression (leukopenia)
  - Nausea and vomiting
  - Stomatitis and diarrhea
Cross-Linkers

• Platinum agents are technically alkylating agents, but have slightly different action
• Cell cycle nonspecific and cause inter- and intra-strand cross-linking
• Examples:
  – Cisplatin
  – Carboplatin
  – Oxaliplatin
Cis-platinum (CDDP)

- Many uses: head and neck, lung, GYN, primary brain tumors
- Great radiation synergy
- Toxicity (many):
  - Neurotoxicity, ototoxicity
  - Nausea and vomiting
  - Myelosuppression
  - Nephrotoxicity
  - Electrolyte disturbances (Ca, Mg, K)
Select Biologic Agents

- Cetuximab (Erbitux)
- Bevacizumab (Avastin)
- Ipilimumab (Yervoy)
- Vemurafenib (Zelboraf)
Cetuximab (Erbitux)

- Recombinant human/mouse monoclonal antibody produced in mouse cell culture
- Indications for HNSCC and colon cancer
- Known to have synergy with radiation therapy
- Primary toxicities
  - Anaphylaxis: 3%
  - Acneiform rash is prognostic and associated with improved outcomes
Bevacizumab (Avastin)

• Humanized Mab against the VEGF-R
  – Felt to serve as a protective agent in those with recurrent GBM receiving re-irradiation
• Stabilizes tumor vasculature and may make more oxygen available
• May also induce more cellular death via an apoptotic pathway
• Generally safe with radiation therapy
Ipilimumab (Yervoy)

- Currently FDA approved for use in metastatic melanoma
- Known to have synergistic activity with radiation therapy
  - “Abscopal Effect” well described in melanoma
  - Retrospective evidence of safety and possible improved outcomes dependent upon sequence of therapy
Vemurafenib (Zelboraf)

- Requires a BRAF V600 mutation, ineffective in wild type tumors
- Dabrafenib/Vemurafenib are FDA approved in the metastatic setting
- Moderately severe skin effects with concurrent irradiation
- Generally avoided with concurrent radiation therapy
Select Toxicities and Management
Radiation Dermatitis

- Our most commonly encountered toxicity
- Can be amplified by certain chemotherapies
  - Cisplatin and 5-FU are common offenders
- Early (acute) reactions commonly resolve
- Late (chronic) reactions can either be stand-alone or as a result of a very severe acute reaction
- Prophylaxis is always a good idea
# Acute Dermatitis Grading

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
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<tbody>
<tr>
<td>Faint erythema or dry desquamation</td>
<td>Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate oedema</td>
<td>Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion</td>
<td>Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site</td>
<td>Death</td>
</tr>
</tbody>
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Management of Dermatitis

• Grade 2/3:
  – OTC creams: aquaphor, cetaphil, desitin
  – Hydrophilic dressings, an anti-inflammatory emulsion (e.g. trolamine, hyaluronic acid cream)
  – Silver sulfadiazine or beta glucan cream
    • Only applied after radiotherapy

• Grade 4: individualized care, may require antibiotics
  – Consider a treatment break
Management of Chronic Fibrosis

• Pentoxiphylline (Trental)/vitamin E
  – May decrease subjective skin fibrosis as well as skin compliance
  – Can cause some nausea, lessened if taken with meals
  – Standardly used at UAB for breast patients considering reconstruction

• Physical therapy is commonly used
  – Necks, chest wall mobility, many soft tissue sites
Mucositis

• Broadly includes upper (mouth, throat, esophagus) and lower (intestines, rectum, anus, bladder)

• Upper sites are managed similarly

• Lower sites are managed depending on site
Oral Mucositis, Esophagitis

- **Early stage:**
  - supportive care, NSAIDs
  - PPIs
  - MMW cocktail: typically viscous lidocaine, maalox, Benadryl but many variations exist

- **More advanced cases:**
  - Steroids (systemic or topical), opioid medications
  - Certain cases may require PEG feedings or IV fluids
  - Glutamine supplements have been shown to help

- Carafate may actually make esophagitis worse
Lower GI Mucositis

• Rectal irritation is common with any pelvic treatment
  – Observation is most commonly appropriate

• Treatment:
  – NSAIDs are first line
  – Rectal steroids or systemic steroids in more advanced cases
  – Laser coagulation can be necessary in late proctitis
Cystitis

• Common with prostate and GYN/GU malignancies

• Treatment:
  – NSAIDs first line, pyridium
  – Anecdotal success with sports drinks (Gatorade, Powerade)
  – Steroids may be necessary when cases are more advanced
Diarrhea

- Acute or chronic toxicity can be a late manifestation in GI, GU, or prostate therapies

- Treatment:
  - First line therapies are Imodium, Lomotil
  - Decrease fiber intake in diet
  - Octreotide can be useful in refractory cases
  - Again, maintain hydration
Pneumonitis

• Associated with cough, SOB, can have fevers
  – Lots of cross-over with infection, often difficult to distinguish

• Some cases can resolve spontaneously, but it is usually progressive in nature

• Treatment:
  – Prednisone 1 mg/kg initially with a very slow taper over 6-8 weeks or longer
  – Consider antibiotics
Neurotoxicity

• Can be as a result of the tumor itself or as a result of treatment
• Acute: most commonly due to edema
• Late: more likely associated with radiation toxicity
Neurotoxicity

• Acute management: presumably due to edema
  – Dexamethasone at 8 mg/day, divided and rapidly tapered if possible

• Late management:
  – Memantine (Namenda) can help with memory function
  – Cumbersome dosing, not widely adopted
In Summary:

• Be aware of what your chemotherapy your patient is taking during radiation
• Prevention is usually easier than treatment  
  – Not always possible
• First-line therapy for early toxicities can be easily managed by nursing staff