Drug-Radiation Interactions
The Radiobiology of Chemotherapy

Brian Czito, MD
2017 Lecture Series

Chemotherapy

- Background
- Biologic basis
- Classes of agents and mode of action
- Dose-response
- Drug resistance
- Clinical evidence and trial design
Chemotherapy milestones

• Term coined by Paul Erhlich - ca 1900 (arsenic-parasite treatment)
• Alkylating agents (WWII) - marrow and lymphoid hypoplasia
• Hodgkin’s disease treatment (Yale 1943)
• Single drugs: (rapidly proliferating tumors)
  • methotrexate - choriocarcinoma, leukemia
  • cyclophosphamide - Burkitt’s lymphoma

5-FU

• 5FU: synthesized in 1957 by Heidleberger
• CMT: 5-FU used since 1960’s
Milestones

• 60’s and 70’s - combination chemo:
  • Acute lymphocytic leukemia
  • Hodgkin’s disease
  • Diffuse histiocytic lymphoma
  • Testicular cancer
• Combined-modality treatment (Chemo, RT, Surgery)

Combination of RT and Chemotherapy

• First attempts:
  – colloidal lead, synthetic Vit.K
  – purine and pyrimidine analogs
• 5-FU trial (Univ. of Wisconsin) oral cavity ca.
• Methotrexate (RTOG) H&N
• Pediatric tumors: (dactinomycin, doxorubicin)
  – Wilms’ tumor
  – Ewing’s sarcoma
  – rhabdomyosarcoma
Radiosensitizers

- Chemical or pharmacologic agents that increase the lethal effects of radiation if administered in conjunction with it.
- Ideally, differential effect between tumors and normal tissues (increase tumor sensitivity to a greater extent than normal cells).

The Basic Strategy of All Radiosensitizers

The addition of drug is expected to move the tumor-control curve to the left but not affect the NTCP curve, or at least alter it as much.
Biologic Basis of Chemotherapy

• Effect on DNA synthesis or function
• Targeting rapidly proliferating cells
• Effectiveness limited by growth fraction (fraction of cells in active cycle)
• Cell-cycle specific agents
  • platinum compounds, taxanes
• Cell-cycle nonspecific agents
  • alkylating agents

Cell-cycle Specific Agents Produce Effects at Different Phases
Classes of Chemotherapeutic Agents

- Alkylating agents
- Antibiotics
- Antimetabolites
- “Miscellaneous” agents
  - platinum complexes
  - procarbazine
  - vinca alkaloids

Alkylating Agents

- Substitute alkyl groups for hydrogen atoms (DNA)
  - Nitrogen mustard derivatives (cyclophosphamide, chlorambucil, melphalan)
  - Ethylenamine derivatives (thiotepa)
  - Alkyl sulfonates (busulfan)
  - Triazine derivatives (dacarbazine)
  - Nitrosoureas (carmustine BCNU, lomustine CCNU, temozolamide)
- Cell-cycle nonspecific
- Cross blood-brain barrier
Antibiotics

- Natural products of soil fungus Streptomyces
- DNA binding - Inhibitors of DNA and RNA synthesis
- Cell-cycle nonspecific
- Doxorubicin, daunomycin (cardiac damage)
- Dactinomycin (inhibits RNA synthesis)
- Bleomycin sulfate (lung injury)
- Mitomycin C - more toxic to hypoxic cells (myelosuppression)

Vinca Alkaloids

- Plant products
- Binding to microtubular proteins - inhibiting microtubule polymerization - mitotic arrest
  - Vincristine sulfate (Oncovin)
  - Vinblastine sulfate (Velban)
**Taxanes**

- Plant product (yew tree)
- Potent microtubule-stabilizing agents - promote microtubule assembly
- Block (prolong) G2/M phase - increase mitotic index
- Paclitaxel (natural product)
- Docetaxel (synthetic)

**Antimetabolites**

- Analogues of normal metabolites
  - Substituting
  - Competing for catalytic enzymes
  - Competing to alter catalytic rate
- Methotrexate - folic acid antagonist - decreases synthesis of thymidine and purine nucleotides
- Cytotoxicity reversed by leucovorin
Antimetabolites

- 5-Fluorouracil: analogue of thymidine
  - Irreversible inhibition of thymidylate synthetase/depletes thymidine
  - Intracellular conversion to active metabolite
  - Incorporates into DNA
  - Inhibits RNA processing
  - GI, breast, HNC
- Cytarbine: analogue of deoxycytidine
  - Competitive inhibitor of DNA polymerase
  - Cell cycle specific
  - Combine with other chemo for AML
5-FU: Background

- Established radiosensitizer: Mechanism remains unclear
- RT: preferentially upregulates tumoral thymidine phosphorylase (TP) in preclinical models
- Byfield: optimal radiosensitization when delivered >24 before \( \rightarrow \) 48 hours following RT (PVI)

Oral Fluoropyrimidines

- Ftorafur (tegafur): 5-FU prodrug with high bioavailability; some unique CNS toxicities/no S advantage to IV 5-FU; not used in US
- UFT: Tegafur + uracil (DPD inhib); tolerable in rectal pts with RT; not approved in US (no advantage vs IV FU/LV in CRC)
Oral Fluoropyrimidines

• S-1: Tegafur (5-FU prodrug) + gimeracil (DPD inhibitor) + oteracil (inhibits FU phosphorylation GI tract, ↓ diarrhea)

Oral Fluoropyrimidines

• Capecitabine: Oral 5FU prodrug; relies on thymidine phosphorylase (TP) → higher levels in some tumors, including CRC → higher FU conc in tumors (vs same with IV FU)
  • → RT upregulates TP
  • Approved in many countries including US
Miscellaneous agents

• Procarbazine: hydrazine derivative
  – mechanism not clear
  – Hodgkin’s disease
• Hydroxyurea: inhibitor of ribonucleotide reductase (cervix, HNC)
  – cytotoxic to cells in S phase
• Cis-platinum
  – binds to DNA: intra and inter strand cross-linking

Angiogenesis and VEGF in Cancer

• Main proangiogenic factor: VEGF
• VEGF: key mediator of angiogenesis
• Overexpressed in most tumors
• Increased VEGF expression associated with advanced tumor stage, disease progression and poor prognosis
• VEGF inhibition suppresses tumor growth in animal models
Phase III bevacizumab Trial

- Patients receiving bevacizumab + IFL had statistically improved Survival (MS-20 mo) versus Patients receiving IFL Only (16 mo)

**Normalization Hypothesis**

*Jain, Nature Medicine (2001)*

*Tong et al. (2003)*

**VEGF Blockade Normalizes Tumor Vasculature**
Willett Trial

- Bevacizumab: Anti-Vascular Effects (↓ IFP, ↓ blood flow/volume, ↓ MVD)
- Support For “Normalization” Hypothesis

Common Antineoplastic Drugs
Sites of Action
Radiosensitization with conventional chemotherapeutic agents.

- combined modality therapy used in the definitive/adjuvant therapy of the majority of cancer patients (head and neck, lung, esophagus, stomach, pancreas and rectal cancer).
- Mechanisms by which conventional chemotherapy produce radiosensitization remain largely unknown.

5-Fluorouracil

- both DNA effects (inhibits thymidylate synthase) and RNA (direct incorporation)
- data suggest radiosensitization is due to thymidylate synthase inhibition
- protracted infusion- pump, capecitabine often preferred from a radiosensitization standpoint.
Gemcitabine

- depletes deoxynucleotide triphosphate pools, potentially explaining its effect as a radiosensitizer.
- inhibition of ribonucleotide reductase is a key step in producing sensitization (hydroxyurea, a pure inhibitor of ribonucleotide reductase, has been used as a radiosensitizer in the treatment of head and necks and cervical cancer).

Cisplatin/Carboplatin and Oxaliplatin

- ? enhanced formation of toxic intermediates in the presence of radiation induced free radicals
- ? Radiation induced increase in cellular platinum uptake.
- ? Inhibition of DNA repair
- ? Cell cycle arrest
Dose-Response Relationships

- Anticancer drugs kill cells by first-order kinetics (given dose kills a constant fraction of a population of cells)
- Inverse relationship between curability and the tumor cell burden
- Sensitivity to cell killing varies enormously among cell type
Wide Variability in Taxane Sensitivity

Tumor Hypoxia

- Radioresistance
- Metastatic disease
- Regulation
  - Oncogenes, tumor suppressor genes, stress proteins, cytokines
- Drug resistance
- Angiogenesis
Adverse Effect of Tumor Hypoxia in H&N Cancer


Oxygen Effect in Chemotherapy Friend or Foe?
Oxygen Effect in Chemotherapy

<table>
<thead>
<tr>
<th>Preferential Toxicity to Aerobic Cells</th>
<th>Preferential Toxicity to Hypoxic Cells</th>
<th>Minimal or No Selectivity Based on Cellular Oxygenation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>Mitomycin-C</td>
<td>5-Fluorouracil¹</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Doxorubicin</td>
<td>Methotrexate²</td>
</tr>
<tr>
<td>Streptonigrin</td>
<td>Misonidazole, metronidazole</td>
<td>Cisplatin</td>
</tr>
<tr>
<td></td>
<td>Etanidazole</td>
<td></td>
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<td></td>
<td>Tirapazamine</td>
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<tr>
<td></td>
<td>RB6145</td>
<td></td>
</tr>
<tr>
<td>Daclomycin</td>
<td>5-thio-D-glucose, 2-deoxy-D-glucose</td>
<td>BCNU, CCNU</td>
</tr>
</tbody>
</table>

Drug Resistance

- Acquired quickly, uniformly and inevitably
- Genetic basis (most forms)
- Resistant clone - gene mutation (chemotherapeutic agents are powerful mutagens)
- Strategy to overcome: multiple agents
- Problem: pleiotropic resistance (cross-resistance) - multi drug resistance
Drug Resistance

• Multidrug resistance - extrusion of the drugs
• Mediated by multiple drug resistance gene (mdr) product: p-glycoprotein (membrane protein)
• mdr gene mapped to human chromosome 7

Drug Resistance

• no relationship between chemoresistance and radioresistance
### Comparison Chemo vs Radiation

- Chemo: greater variation in sensitivity
- Drug sensitivity can be manipulated to a greater extent than RT
- Oxygen effect more complex
- Resistance develops more quickly and regularly

### Combining Chemo and RT Strategies

- Adjuvant
- Induction (neoadjuvant) chemotherapy
- Concurrent chemotherapy
Methods of Delivery

• Sequential
  Neoadjuvant or adjuvant chemo

• Alternating
  RT CT RT CT RT

• Concurrent
  Both agents given simultaneously

Rationale
Improve Therapeutic Ratio

• Kill tumor cells outside of the treatment field (adjuvant)
• Kill tumor cells inside of the treatment field (additive effect)
• Sensitize tumor cells in the treatment field (concurrent Rx)
Specific Sites

- Anal
- Esophagus
- Rectal
- Head and Neck
- Cervix
- Small Cell Lung
- Breast

Esophageal Cancer

Non-Operable Esophageal Cancer

ChemoRT (50 Gy + 5-FU/CDDP) vs RT Only (64 Gy) (8501)
ChemoRT vs RT Only (8501)

CMT provides long term survival of ~ 30% and is superior to high dose RT only.

Operable Esophageal Ca: Neoadjuvant ChT vs Neoadjuvant CMT

- Phase III (German) POET Study
- T3-4 esophagogastic adeno randomized:
  1) Cis/5FU/FA → S
  2) Cis/5FU/FA → Cis/Etop/30 Gy - 2 Gy fxs → S

Closed early-poor accrual (126/354 planned pts)
Not sufficiently powered to detect a difference.
### Operable Esophageal Ca: Neoadjuvant ChT vs CMT

<table>
<thead>
<tr>
<th></th>
<th>R0</th>
<th>pCR</th>
<th>N0</th>
<th>Med OS</th>
<th>OS3 OS</th>
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</thead>
<tbody>
<tr>
<td>Chemo-Surg</td>
<td>77%</td>
<td>2%</td>
<td>37%</td>
<td>21 mo</td>
<td>28%</td>
</tr>
<tr>
<td>CMT-Surg</td>
<td>85%</td>
<td>16%*</td>
<td>64%*</td>
<td>33 mo</td>
<td>47%**</td>
</tr>
</tbody>
</table>

*p=.07, HR .67

Stahl JCO 2009

### Esophageal Cancer: Future Studies US

Operable

Novel CMT regimens (trastuzumab for HER2 + pts)
RTOG 1010: Phase III Study of Neoadjuvant Trastuzumab and Chemoradiation for Esophageal/GEJ Adenocarcinoma

- CHEMORADIATION (Carbo/Taxol)
- HER-2 (+) (FISH)
- TRASTUZUMAB + CHEMORADIATION
- SURGERY
- SURGERY + TRASTUZUMAB (1 YR)

Anal Cancer
RT ± chemo: UKCCCR/ACT I

Trial Schema:

585 pts
1987-1994
anal canal or margin

Primary endpoint:
Local control
Secondary endpoint:
5-yr OS

45 Gy + boost
N=290

45 Gy + boost + 5FU+MMC
N=295

Median FU:
12 years

UKCCCR, Lancet 1996
Northover, Br J Cancer 2010

UKCCCR: local failure

Percentage of patients having a loco-regional relapse (%)

5-year: ~24.8% (~17.1 to 31.3)
10-year: ~25.3% (~17.5 to 32.0)
12-year: ~25.3% (~17.5 to 32.0)

Time since randomisation (years)

RT alone
CMT

Northover, Br J Cancer 2010
EORTC: endpoints

Locoregional control

- RT
- RT+CX

Δ = 18%
p = 0.02

Colostomy-free survival

- RT
- RT+CX

Δ = 32%
p = 0.002

• No OS5 difference (57% v. 52%, p = 0.17)

Bartelink, J Clin Oncol 1997

RTOG 87-04

Trial Schema:

291 pts
1988-1991

Primary endpoints:
Post-tx biopsy
Colostomy rate

Salvage: 6wks bx + CRT (9Gy) + 4wk bx + APR

45-50.4Gy+5FU
N=145

45-50.4Gy+5FU + MMC
N=146

Median FU: 36 months

Flam, J Clin Oncol 1996
RTOG 87-04

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>Complete Pathological Response</th>
<th>Local Regional Recurrence</th>
<th>Cystectomy-free Survival</th>
<th>Disease-free Survival</th>
<th>Overall Five-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation therapy plus fluorouracil</td>
<td>145</td>
<td>15</td>
<td>36</td>
<td>58</td>
<td>50</td>
<td>65</td>
</tr>
<tr>
<td>Radiation therapy plus fluorouracil and mitomycin</td>
<td>146</td>
<td>8</td>
<td>17</td>
<td>64</td>
<td>67</td>
<td>67</td>
</tr>
</tbody>
</table>

P value: 0.06 < 0.001 0.09 < 0.003 0.41

*Data are from Flam et al.* Median follow-up was 60 months. Nineteen of the original 310 patients were excluded from the analysis.

RTOG 98-11

682 pts
Multicenter
1998-2005
Stratified by sex, nodal status, tumor size

Primary endpoint: 5-yr DFS

Randomize

Concurrent CRT
5FU+MMC
RT 45-59 Gy

Induction:
5FU+CDDP
x 2 cycles

Concurrent CRT
5FU+CDDP
RT 45-59 Gy

Median FU:
30 months

Ajani, JAMA 2008
Neoadjuvant Cisplatin Chemotherapy Before Chemoradiation: A Flawed Paradigm?
Rob Glynn-Jones and Peter Hoskin

RTOG 98-11: Update

<table>
<thead>
<tr>
<th>Treatment</th>
<th>DFS5</th>
<th>OS5</th>
<th>CFS5</th>
</tr>
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<tbody>
<tr>
<td>RT+5FU/MMC</td>
<td>67.7%</td>
<td>78.2%</td>
<td>71.8%</td>
</tr>
<tr>
<td>RT+5FU/CDDP</td>
<td>57.6%</td>
<td>70.5%</td>
<td>64.9%</td>
</tr>
<tr>
<td>P value</td>
<td>0.0045</td>
<td>0.021</td>
<td>0.053</td>
</tr>
</tbody>
</table>
Ongoing RT Trials

- France: Phase II Cisplatin + 5FU With Cetuximab
- US (AMC): Phase II Cisplatin + 5FU + Cetuximab in HIV-Associated Anal Carcinoma
- US (ECOG): Phase II Trial of Cisplatin + 5FU + Cetuximab

Rectal
### Postoperative Randomized Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Local Failure</th>
<th>Distant Failure</th>
<th>Overall Survival</th>
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<tbody>
<tr>
<td><strong>GITSG (1986)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>24</td>
<td>34</td>
<td>28</td>
</tr>
<tr>
<td>Surgery Chemo</td>
<td>27</td>
<td>27</td>
<td>43</td>
</tr>
<tr>
<td>Surgery Radiation</td>
<td>20</td>
<td>30</td>
<td>43</td>
</tr>
<tr>
<td>Surgery Chemoradiation</td>
<td>11</td>
<td>26</td>
<td>57</td>
</tr>
<tr>
<td><strong>NSABP R-01 (1988)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>25</td>
<td>26</td>
<td>48</td>
</tr>
<tr>
<td>Surgery Chemo</td>
<td>21</td>
<td>24</td>
<td>58</td>
</tr>
<tr>
<td>Surgery Radiation</td>
<td>16</td>
<td>31</td>
<td>50</td>
</tr>
<tr>
<td><strong>NCCCG/Mayo (1991)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery Radiation</td>
<td>25</td>
<td>46</td>
<td>38</td>
</tr>
<tr>
<td>Surgery Chemoradiation</td>
<td>14</td>
<td>29</td>
<td>53</td>
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</table>
Postoperative Randomized Trials

<table>
<thead>
<tr>
<th>Survival</th>
<th>Local Failure</th>
<th>Distant Failure</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intergroup (1992)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery ChemoRT</td>
<td>-</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>(Bolus 5FU)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery Chemo RT</td>
<td>-</td>
<td>31</td>
<td>70</td>
</tr>
<tr>
<td>(PVI 5FU)</td>
<td></td>
<td></td>
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</tbody>
</table>

EORTC 22921

Pre-op RT

Post-op 5FU/LV x4

Surgery

Post-op RT + 5FU/LV x2

Surgery

Pre-op RT + 5FU/LV x2

Surgery

Pre-op RT

Surgery

Accrual: 1011 patients
April 1993 - April 2003

Bosset New Eng J Med 2006
### EORTC 5-Year Outcomes

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>CT RT</th>
<th>-Adj CT</th>
<th>+Adj CT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute toxicity G3/4</strong></td>
<td>7%</td>
<td>14% *</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Post-op toxicity</strong></td>
<td>23%</td>
<td>23%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>pCR rate</strong></td>
<td>5%</td>
<td>14% *</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sphincter preserv</strong></td>
<td>51%</td>
<td>53%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Local recurrence</strong></td>
<td>17%</td>
<td>9% *</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td>65%</td>
<td>66%</td>
<td>63%</td>
<td>67%</td>
</tr>
</tbody>
</table>

### FFCD 9203

**Arm A**
- RT 45 Gy
- CT CT CT CT

**Arm B**
- RT 45 Gy
- 5-FU d1-5, 29-33
- CT CT CT CT


Gerard J Clin Onc 2006
# FFCD 5-Year Outcomes

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>CT RT</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute toxicity G3/4</strong></td>
<td>3%</td>
<td>15%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Post-op toxicity</strong></td>
<td>27%</td>
<td>21%</td>
<td>NR</td>
</tr>
<tr>
<td><strong>pCR</strong></td>
<td>4%</td>
<td>11%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Sphincter preserv</strong></td>
<td>54%</td>
<td>52%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Local failure</strong></td>
<td>17%</td>
<td>8%</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td>68%</td>
<td>67%</td>
<td>NS</td>
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</table>

## Study Patient # Regimen Pathologic complete response rate Gr 3-4 Toxicity

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient #</th>
<th>Regimen</th>
<th>Pathologic complete response rate</th>
<th>Gr 3-4 Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(STAR)-01</td>
<td>741</td>
<td>RT + 5-FU</td>
<td>16%</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT + 5-FU + Oxaliplatin</td>
<td>P=.98</td>
<td>P&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15%</td>
<td>24%</td>
</tr>
<tr>
<td>ACCORD 12/0405</td>
<td>598</td>
<td>RT + Capecitabine</td>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>PRODIGE 2</td>
<td></td>
<td>RT + Capecitabine + Oxaliplatin</td>
<td>P=.09</td>
<td>P&lt;.001</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>19%</td>
<td>25%</td>
</tr>
<tr>
<td>Study</td>
<td>Patient #</td>
<td>Regimen</td>
<td>Pathologic complete response rate</td>
<td>Gr 3-4 Toxicity</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------</td>
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</tr>
<tr>
<td>(STAR)-01</td>
<td>741</td>
<td>RT + 5-FU</td>
<td>16% P=.98 15%</td>
<td>8% P&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT + 5-FU + Oxaliplatin</td>
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<tr>
<td>ACCORD 12/0405</td>
<td>598</td>
<td>RT + Capecitabine</td>
<td>14% P=.09 19%</td>
<td>11% P&lt;.001</td>
</tr>
<tr>
<td>PRODIGE 2</td>
<td></td>
<td>RT + Capecitabine + Oxaliplatin</td>
<td></td>
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</tr>
</tbody>
</table>

Survival Benefit of Concurrent Chemoradiation

Meta-analysis: 87 trials; >12,000 patients

- 19% death risk reduction
- p<0.0001

Platinum most important agent

*Survival: 50% at 2 years and 32% at 5 years in control groups.
Radiation Sensitization: New Agents and trial design

- Capecitabine ("Oral 5-FU")
  - Thymidylate synthetase inhibition
- Irinotecan
  - Topoisomerase I inhibition
- Oxaliplatin
  - Inter/intra-strand DNA crosslinks
- Anti-EGFR: Cetuximab, Panitumumab, Gefitinib, Erlotinib
- Anti-VEGF: Bevacizumab
- PARP inhibitors
- PD-1, PD-L1 Inhibitors

EGFR

- Overexpression: poor prognosis/radiation therapy resistance
- Radiation synergy in preclinical models, head and neck cancers
- GI cancers→ unknown efficacy/tolerability with differing local tissue tolerances
Systemic Therapy

• Oxaliplatin
  – New generation platinum analog
  – Radiation-enhancing effects in vitro

• Panitumumab
  – Humanized monoclonal EGFR antibody
  – Potentiates chemotherapy and radiation tumor cytotoxicity in preclinical models

Example

Phase I/II Trial: RT, Panitumumab, Oxaliplatin & Capecitabine

**Study Objectives**

• Define MTD and/or recommended phase II dose
• Describe frequency and nature of toxicities
• Estimate clinical & pathological CR rates
Inclusion Criteria

• SCC/adenocarcinoma of the esophagus or proximal stomach
• T1-4, N0-2, M0-1
• ECOG Performance Status 0-1
• Measurable disease
• Meet lab criteria

Trial Schema

Screening & Registration
CT; PET; EGD/ EUS; bronchoscopy and j-tube (as indicated)

XRT/Chemo (weeks 1-5.5)

Restaging (week 9.5)
CT CAP; PET; EGD

SD, PR or CR (Surg Evaluation)  PD (Individualize Tx)
**Chemoradiotherapy Schema**

```
2 weeks          5.5 weeks          4 weeks

Chemoradiotherapy

Staging

Repeat Staging

Surgery (if indicated)
```

**Dose Escalation**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>XRT (cGy)</th>
<th>Oxaliplatin (mg/m2) D 1,8,15, 22,29,36</th>
<th>Cape (mg/m2/bid) M-F</th>
<th>P-mab (mg/kg) D 1,15,29</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>5040</td>
<td>30</td>
<td>500</td>
<td>3.6</td>
</tr>
<tr>
<td>1</td>
<td>5040</td>
<td>40</td>
<td>625</td>
<td>3.6</td>
</tr>
<tr>
<td>2</td>
<td>5040</td>
<td>50</td>
<td>825</td>
<td>4.8</td>
</tr>
<tr>
<td>3</td>
<td>5040</td>
<td>50</td>
<td>825</td>
<td>6.0</td>
</tr>
</tbody>
</table>
**Dose Escalation Scheme**

- An exposure-adjusted, continual reassessment methodology was used to identify MTD and subsequent RPTD based on observed toxicities.

**Dose Limiting Toxicity**

- Gr 3-4 non-heme tox > 7 days despite adequate support
- Any Gr 3-4 heme tox > 7 days
- Neutropenic fever
- Gr 4 lab abnormalities
- Treatment related death or hospitalization
- Inability to deliver ≥ 80% of planned treatment doses
Dose Escalation

• Phase I: up to 18 pts
• Phase II: up to 20 additional pts

Phase I DLTs

• 1: dehydration, FTT → hospitalization
• 2: probable drug reaction (rigors, fever, vomiting, ↓ BP) → hospitalization
• non-DLT toxicities: Acneform rash, electrolyte imbalances, lower ext edema

• Phase I: 9 pts
• Phase II: 20 pts
Gr 3 Toxicities (all pts)

- Anorexia 5/29 (17%)
- Dysphagia 3/29 (10%)
- Nausea 7/29 (24%)
- Vomiting 3/29 (10%)
- Dehydration 3/29 (10%)
- Common Gr 1-2 tox:
  - Rash, N/V, fatigue, esophagitis, sensory neuropathy
- No Gr 4 tox nor tx related deaths

Response outcomes: All pts

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGD</td>
<td>55%</td>
<td>35%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>PET</td>
<td>41%</td>
<td>38%</td>
<td>7%</td>
<td>10%</td>
</tr>
</tbody>
</table>

- Esophagectomy: 20/29 (69%) pts
- 8/20 (40%) pN+
- Primary site pCR: 45% patients
  - 2 had microscopic (< 5mm and < 1 mm focus) nodal involvement
Postoperative period

• Anastomotic leak: 7 pts (35%)
  – Reoperation: 2 pts
  – Stent placement: 3 pts

Worth carrying to next level/phase II-III?
Wales Cancer Trials Unit

Cisplatin, Capecitabine, and Radiation Therapy With or Without Cetuximab in Treating Patients With Esophageal Cancer (SCOPE Trial)

- The use of cetuximab was associated with greater toxicity, lower doses of dCRT and worse survival! More is not always better!

Esophageal Cancer: Studies US

Inoperable

Intergroup: EBRT + Paclitaxel / CDDP ± C225

Further accrual halted
Study | Patient # | Regimen | Pathologic complete response rate
--- | --- | --- | ---
Memorial Sloan Kettering | 20 | Cetux, 5-FU, 50.4 Gy | 12%
Modena | 38 | Cetux, 5-FU, 50.4 Gy | 8%
Louvain | 40 | Cetux, Cape, 45 Gy | 5%
German Multi-site | 60 | Cetux, Cape, Ox, 50.4Gy | 9%
Heidelberg | 50 | Cetux, Ir, Cape, 50.4Gy | 8%
Slovenia | 37 | Cetux, Cape, 45 Gy | 8%
Goyang | 39 | Cetux, Ir, Cape, 50.4Gy | 23%
EXPERT-C Multi-site | 83 | Cetux, Cape, 45 Gy | 18%

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**Poly(ADP-Ribose) Polymerase (PARP)**

- A group of nuclear enzymes that recognizes DNA damage and facilitates DNA repair
- A key role in the repair of DNA single-strand breaks
- Through the base excision repair pathway (BER)
- Binds directly to sites of DNA damage
- Once activated, generates large, branched chains of poly (ADP-ribose) polymers on multiple target proteins
- Recruits other DNA repair enzymes
**Inhibiting PARP-1 Increases Double-Strand DNA Damage**

- DNA single strand break (SSB) damage
- Inhibition of PARP-1 prevents recruitment of DNA repair enzymes
- leads to failure of SSB repair
- accumulation of SSBs
- During S-phase, replication fork is arrested at site of SSB

**Study Objectives**

- **Primary:** determine MTD/ RPTD of veliparib/ capecitabine/RT in locally advanced rectal cancer

- **Secondary:** assess safety/tolerability, pharmacokinetic profile and preliminary efficacy (pCR rate, rate of sphincter sparing)
Veliparib-RT Rectal

- Study Population
  - Adult patients (≥18 years of age) with newly diagnosed, histologically-confirmed, locally advanced (T3, T4, or any T with N1 or N2, and M0) adenocarcinoma of the rectum staged by trans-rectal ultrasound or magnetic resonance imaging
  - Dose limiting toxicities (DLTs)
  - DLTs will be assessed from Week 1 Day 2 through 2 weeks after the last day of radiation

Tumor Response

<table>
<thead>
<tr>
<th>Response</th>
<th>Veliparib dose, mg BID</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;400 (n = 16)</td>
<td>400 (n = 15)</td>
</tr>
<tr>
<td>ypCR</td>
<td>4 (25)</td>
<td>5 (30)</td>
</tr>
<tr>
<td>Tumor downstaging</td>
<td>12 (75)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>Sphincter-sparing surgery</td>
<td>11 (69)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>CEA response rate</td>
<td>12 (75)</td>
<td>9 (60)</td>
</tr>
</tbody>
</table>

BID, twice daily; CEA, carcinoembryonic antigen; ypCR, pathologic complete response. 1 patient withdrew consent, so only 31 patients were evaluated for efficacy.
NRG-GI002 (TNT) Schema
Non-comparative experimental arms

Locally Advanced Rectal Cancer

- FOLFOX x 8 → XRT + Capecitabine → Surgery
- FOLFOX x 8 → XRT + Capecitabine + Veliparib → Surgery
- FOLFOX + ? → XRT + Capecitabine + ? → Surgery

Additional arms added through protocol amendments

Conclusions

- Chemotherapy: Many different classes & mechanisms
- Important radiosensitizers although mechanism not always clear
- Ongoing studies: Newer generation chemo (oxali, cape) + targeted agents (bevacizimab, EGFR inhibitors, PARP, PD-1)
- Ongoing study with radiation therapy
Conclusions

• Toxicity (Acute and Late): Important Consideration
• Toxicity will likely increase with new agents with template of EBRT
• Careful radiation planning important
• More is not always better