Colorectal Cancer Therapy and Associated Toxicity

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University of Colorado
GI Cancers Are Common

2009 Estimated U.S. Cancer Deaths

Available at: http://www.cancer.org.

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Men 292,540</th>
<th>Women 269,800</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung and bronchus</td>
<td>30%</td>
<td>26%</td>
</tr>
<tr>
<td>Prostate</td>
<td>9%</td>
<td>15%</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Liver/bile duct</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td>23%</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Colorectal cancer represents 2\textsuperscript{nd} leading cause of death

Available at: http://www.cancer.org.
Goals

• Define Therapeutic Groups

• Discuss Treatment Options

• Discuss Treatment Related Toxicity & Management

• Discuss Cancer Surveillance Options
Colon Cancer Staging
## Prognosis

<table>
<thead>
<tr>
<th>Numerical</th>
<th>Stage TNM</th>
<th>Description</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1,2 N0 M0</td>
<td>Into submucosa and muscularis</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>II</td>
<td>T3,4 N0 M0</td>
<td>Into or through serosa; may attached to nearby tissue</td>
<td>85%</td>
</tr>
<tr>
<td>III</td>
<td>TX N1,2 M0</td>
<td>Invades regional nodes</td>
<td>28-74%</td>
</tr>
<tr>
<td>IV</td>
<td>TX NX M1</td>
<td>Distant mets</td>
<td>5-11%</td>
</tr>
</tbody>
</table>
Treatment Options

• **Adjuvant Therapy**
  - Stage II High Risk and III
  - High Risk Features
    - Grade 3 or 4
    - Lymphovascular invasion
    - Bowel obstruction
    - < 12 lymph nodes dissected
    - indeterminant or positive margins
    - perforation

• **Systemic Therapy – Metastatic Disease**
### Colorectal Cancer Treatment Options

#### “Cytotoxics”

<table>
<thead>
<tr>
<th>Cytotoxics</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 5-Fluorouracil (5-FU)</td>
<td>-&gt; pyrimidine analog</td>
</tr>
<tr>
<td>2. Capecitabine (Xeloda)</td>
<td>-&gt; oral 5-FU pro-drug</td>
</tr>
<tr>
<td>3. Irinotecan (Camptosar)</td>
<td>-&gt; topoisomerase I inhibitor</td>
</tr>
<tr>
<td>4. Oxaliplatin (Eloxatin)</td>
<td>-&gt; 3rd generation platinum</td>
</tr>
</tbody>
</table>

#### “Biologics”

<table>
<thead>
<tr>
<th>Biologics</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cetuximab (Erbitux)</td>
<td>-&gt; antibody against EGFR Epidermal Growth Factor Receptor</td>
</tr>
<tr>
<td>2. Panitumumab (Vectibix)</td>
<td>-&gt; antibody against EGFR</td>
</tr>
<tr>
<td>3. Bevacizumab (Avastin)</td>
<td>-&gt; antibody against VEGF Vascular Endothelial Growth Factor</td>
</tr>
</tbody>
</table>
Proposed Mechanism of Action of Cetuximab (Erbitux)

ERBITUX package insert, February 2004
Blood Vessels and Tumor Growth

• Solid tumors cannot grow beyond 1 to 2 mm$^3$ without an increase in blood supply via new vessel formation\(^1\)

• “Angiogenesis” is thus required for tumor growth and metastasis\(^1\)

• Inhibition of tumor angiogenesis leads to tumor cell growth arrest, death of tumor cells, and in some cases, tumor regression\(^2\)

Tumor angiogenesis is stimulated...

New vessels then facilitate tumor growth.

Courtesy of Novartis Oncology
VEGF: A Central Mediator of Angiogenesis

Environmental factors¹ (hypoxia, pH)
Growth factors, hormones¹ (EGF, bFGF, PDGF, IGF-1, IL-1α, IL-6, estrogen)

Genes involved in tumorigenesis¹,³ (p53, p73, src, ras, vHL, bcr-abl)

Binding and activation of VEGF receptor²

Endothelial cell activation²

Survival  Proliferation  Migration

ANGIOGENESIS

Role of K-ras in CRC Therapy
EGFR – Ras Signal Transduction
A Mutated K-ras

No. at Risk
Cetuximab plus best supportive care 75 19 7 3
Best supportive care alone 76 26 9 4

B Wild-type K-ras

No. at Risk
Cetuximab plus best supportive care 110 68 44 24 8 5
Best supportive care alone 105 41 33 2 1 1

A Mutated K-ras

Overall Survival (%)

P = 0.89

No. at Risk
Cetuximab plus best supportive care 75 67 45 26 15 10 7 4
Best supportive care alone 76 64 39 26 19 12 10 7

B Wild-type K-ras

Overall Survival (%)

P = 0.001

No. at Risk
Cetuximab plus best supportive care 110 101 88 75 48 31 19 8
Best supportive care alone 105 88 65 34 23 17 12 5
Therapy for Advanced Colorectal Cancer: Response rates and survival

**First Line**
- FOLFOX or
- CAPOX or
- FOLFIRI
  +/- Bevacizumab

**Second Line**
- FOLFOX or
- FOLIRI or
- Irinotecan alone
- Irinotecan/Cetuximab - Panitumumab
  +/- Bevacizumab

**Third Line**
- Irinotecan + Cetuximab
- Cetuximab

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**Response Rates in Randomized Trials:**
- 30-60%
- 5-15%
- 10-20%

**Survival Benefit in Randomized Trials:**
- Yes
- Yes
- Yes
Incremental Survival Advantage in First-Line Metastatic Colorectal Cancer

- No active drug: ~4-6 mo
- 5-FU/LV: 12-14 mo
- IFL: ~15-16 mo
- FOLFOX4: ~20 mo
- IFL + bevacizumab: 20.3 mo
- FOLFOX/FOLFIRI: 21.5 mo
- FOLFOX/FOLFIRI + biologics: ?

Median OS (mo)
Chemotherapy Toxicity

- **5-FU**
  - Bone Marrow Suppression
  - GI Toxicity
  - Hand and Foot Syndrome
  - Cardiovasospasm
  - Ocular Toxicity

- **Irinotecan**
  - Bone Marrow Suppression
  - Diarrhea
  - Alopecia

- **Oxaliplatin**
  - Bone Marrow Suppression
  - Neuropathy
    - Acute
    - Chronic
Bevacizumab Toxicity

- Hypertension
- Impaired Wound Healing
- RPLS - Reversible Posterior Leukoencephalopathy Syndrome

NEJM 354:980, 2006
EGFR Toxicity

Skin – Rash
Kidney – Hypomagnesemia
GI - Diarrhea
## Early Stage Surveillance

### Table 1. Surveillance Recommendations

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<thead>
<tr>
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<tbody>
<tr>
<td>History and physical exam</td>
<td>Every 3 months for 1 year then every 6 months to 5 years</td>
<td>Every 3 to 6 months for 3 years; then every 6 months to 5 years</td>
<td>Every 3 to 6 months for 2 years then every 6 months to 5 years</td>
</tr>
<tr>
<td>CEA</td>
<td>Every 3 months for 1 year then every 6 months to 5 years</td>
<td>Every 3 months for 3 years*</td>
<td>Every 3 to 6 months for 2 years then every 6 months to 5 years†</td>
</tr>
<tr>
<td>Chest screening</td>
<td>CXR every 6 months for 2 years then every 1 year to 5 years</td>
<td>CT chest every 1 year for 3 years‡</td>
<td>CT chest every 1 year for 3 years§</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Annual exam if positive for neoplasm; exam every 2 years if negative</td>
<td>At 3 years and if results are normal, then every 5 years</td>
<td>At 1 year, 3 years, and 5 years if negative¶</td>
</tr>
<tr>
<td>CT abdomen</td>
<td>At discretion of physician for symptoms, signs, or increased h CEA</td>
<td>CT every 1 year for 3 years‡</td>
<td>CT abdomen/pelvis every 1 year for 3 years§</td>
</tr>
</tbody>
</table>

Abbreviations: COST, Clinical Outcomes of Surgical Therapy; ASCO, American Society of Clinical Oncology; NCCN, National Comprehensive Cancer Network; CEA, carcinoembryonic antigen; CXR, chest x-ray; CT, computed tomography.

* If the patient is a candidate for surgery or systemic therapy.
† If patient is a potential candidate for further intervention.
‡ For patients who are at a higher risk of recurrence and who could be candidates for curative intent surgery.
§ For patients at high risk for recurrence; CT scan may be useful for patients at high risk for recurrence (eg, lymphatic or venous invasion by tumor, or poorly differentiated tumors).
¶ Colonoscopy in 1 year except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 months; if abnormal, repeat in 1; if no advanced adenoma (villous polyp, polyp > 1 cm, or high grade dysplasia, repeat in 3 years, then every 5 years.

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J Clin Oncol 27:3671, 2009
Surveillance

J Clin Oncol 27:3671, 2009
Surveillance

- Diagnosis by CEA only
- Diagnosis by CT scan, chest x-ray, or colonoscopy

Number of Recurrences Detected vs. Year of Follow-Up

J Clin Oncol 27:3671, 2009
Summary

• Colon cancer outcomes have improved with addition of biologic therapies

• Chemotherapy side effects are manageable

• Aggressive surveillance does impact survival