Perioperative Chemotherapy for Colorectal Cancer: Promise and Pitfalls

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Conflict of Interest:

1. No pharma speaker’s bureaus, stock ownership, royalties, etc

2. Career Development Award (2003-2006 Johns Hopkins research support) from Amgen Oncology Institute (Vectibix™)

3. Participated in Scientific Advisory Boards with Genentech (Avastin™), Sanofi-Aventis (Oxaliplatin™)

4. Off-label use of multiple drugs will be discussed
Colorectal Cancer: Chemotherapy

Outline:

1. Brief background
2. Adjuvant chemotherapy for colon cancer
3. Chemotherapy for advanced colorectal cancer
4. Metastectomy issues
Colorectal Cancer is Common

2008 Estimated U.S. Cancer Deaths

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung and bronchus</td>
<td>31%</td>
</tr>
<tr>
<td>Prostate</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Colon and rectum</strong></td>
<td><strong>8%</strong></td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
</tr>
<tr>
<td>Liver/bile duct</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney</td>
<td>3%</td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
</tr>
<tr>
<td>Men</td>
<td>294,120</td>
</tr>
<tr>
<td>Women</td>
<td>271,530</td>
</tr>
</tbody>
</table>

26% Lung and bronchus
15% Breast
9% **Colon and rectum**

6% Pancreas
6% Ovary
4% Non-Hodgkin lymphoma
3% Leukemia
3% Uterine corpus
2% Brain/other nervous system
2% Liver/bile duct
25% All other sites

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

Available at: http://www.cancer.org.
# 7 Drugs for Colorectal Cancer

<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; 3&lt;sup&gt;rd&lt;/sup&gt; generation platinum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>“Biologics”</th>
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<td>1. Cetuximab (Erbitux)</td>
<td>-&gt; antibody against EGFR</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</td>
</tr>
</tbody>
</table>

*Epidermal Growth Factor Receptor*

*Vascular Endothelial Growth Factor*
### Chemotherapy for Colorectal Cancer

#### Combination Regimens: Terminology

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLF-</td>
<td>Leucovorin <em>(FOLinic acid)</em> / infusional 5-FU</td>
</tr>
<tr>
<td>FOLF-OX</td>
<td>+ oxaliplatin <em>(Eloxatin)</em></td>
</tr>
<tr>
<td>FOLF-IRI</td>
<td>+ irinotecan <em>(Camptosar)</em></td>
</tr>
<tr>
<td>FOLFOX</td>
<td>= infusional 5-FU/LV <em>(two days)</em> + oxaliplatin</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>= infusional 5-FU/LV + irinotecan</td>
</tr>
<tr>
<td>CAP-</td>
<td>Capecitabine <em>(Xeloda)</em></td>
</tr>
<tr>
<td>CAP-OX</td>
<td>= XELOX = capecitabine + oxaliplatin</td>
</tr>
<tr>
<td>CAP-IRI</td>
<td>= XELIRI = capecitabine + irinotecan</td>
</tr>
</tbody>
</table>
History of Treatment for Colorectal Cancer

- ~1960: 5-FU is a cornerstone of first-line therapy; bolus/infusion
- ~1985: Addition of LV (biomodulator) to 5-FU bolus regimens
- 1998: Irinotecan as single agent approved as second-line
- 2000: Irinotecan approved as first-line in CRC (bolus IFL)
- 2001: Capecitabine approved as first-line in CRC in selected pts
- 2002: Oxaliplatin approved as second-line agent (FOLFOX)
- 2004: Oxaliplatin approved as first-line agent in infusional regimen
- 2004: Approval of Cetuximab (Erbitux) & Bevacizumab (Avastin)
- 2006: Approval of Panitumumab (Vectibix)

“Approved” = US FDA Approval
capecitabine = Xeloda; irinotecan = camptosar; oxaliplatin = Eloxatin
IFL = irinotecan/5-FU/LV; FOLFOX = 5-FU/LV/Oxaliplatin
Incremental Survival Advantage in First-Line Metastatic Colorectal Cancer

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

Are we hitting a wall with current drugs?
Colorectal Cancer: Chemotherapy

Outline:

1. Brief background
2. Adjuvant chemotherapy for colon cancer
3. Chemotherapy for advanced colorectal cancer
4. Metastectomy issues
Options for “Adjuvant” Chemotherapy for Resected (Primary) Colon Cancer:

1. 5-Fluorouracil/Leucovorin (intravenous) (bolus monthly, bolus weekly, or infusional)
   - Moertel, 1990; Haller, 2005; others

2. 5-Fluorouracil/Leucovorin/Oxaliplatin
   - FOLFOX: Andre, “MOSAIC” Trial
   - FLOX: Wolmark, NSABP C-07

3. Capecitabine (pro-drug of 5-FU)
   - Twelves, “X-ACT” Trial
Adjuvant Therapy for Resected 1°

“MOSAIC” Trial

n = 2,246
Stage II/III colon CA
Primary endpoint:
3-yr disease free
survival (DFS)

“LV5FU2” x 12
(infusional 5-FU/LV)

“FOLFOX4” x 12
(infusional 5-FU/LV with oxaliplatin)

Andre, NEJM 2004
De Gramont, ASCO 2007 (updated 6-year results)
MOSAIC Trial: Disease-Free Survival

Adding a 3rd drug, oxaliplatin, helps improve the cure rate

Data cut-off: June 2006

De Gramont, ACSO 2007
MOSAIC Trial: Overall Survival

No benefit overall for stage II patients (no lymph nodes involved)

HR [95% CI]

Stage II 1.00 [0.71–1.42]

Stage III 0.80 [0.66–0.98]

Overall survival (months)

Data cut-off: January 2007

De Gramont, ACSO 2007
Adding oxaliplatin is more efficacious, but more toxic than 5-FU alone:

Severe (Grade 3/4) Toxicities (FOLFOX vs LV5FU2)
- Low blood counts (40% vs 5%)
- Fever and low blood counts (1.8% vs 0.2%)
- Nausea/Vomiting (6% vs 1.5%)
- Allergic reactions (3% vs 0.2%)
- Neuropathy (sensitivity to cold, numbness and tingling) (12.4% vs 0.2%)

- NOT more toxic deaths

Andre, NEJM 2004
Adjuvant Therapy for Resected 1°
Oxaliplatin added to weekly 5-FU/LV

**NSABP C-07**

- n = 2,407
- Stage II/III colon CA
- Primary endpoint: 3-yr disease free survival (DFS)

**Weekly 5-FU/LV**
- (“Roswell Park”)
- three 8-week cycles

**“FLOX”**
- (above regimen + biweekly oxaliplatin)

Kuebler, JCO 2007
C-07 Trial: Disease-Free Survival

- **FLOX** (1,200 patients, 308 events, 25.7%)
- **FULV** (1,207 patients, 369 events, 30.6%)

**Hazard ratio**: 0.80, 95% CI (0.69 to 0.93), $P^* = .0034$

*Stratified for positive nodes (0, 1-3, ≥ 4)*

**Time After Random Assignment (years)**

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>FLOX</th>
<th>FULV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,082</td>
<td>966</td>
<td>675</td>
</tr>
<tr>
<td>966</td>
<td>675</td>
<td>340</td>
</tr>
<tr>
<td>921</td>
<td>638</td>
<td>291</td>
</tr>
</tbody>
</table>

Kuebler, JCO 2007
Adjuvant Therapy for Resected 1°

C-07 had very similar results compared to MOSAIC:

<table>
<thead>
<tr>
<th></th>
<th>3 yr DFS</th>
<th>Diff</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>C 07</td>
<td>76.5%</td>
<td>4.9%</td>
<td>0.80</td>
</tr>
<tr>
<td>MOSAIC</td>
<td>77.9%</td>
<td>5.1%</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Thus, benefit of oxaliplatin does not appear to depend on schedule of 5-FU/LV.

Wolmark, ACSO 2005
Adding **irinotecan** to 5-FU/LV has not been as efficacious

**Accord 02/FFCD9802** (Ychou, ASCO 2005 #3502)
Added irinotecan to LV5FU2 in high-risk stage III patients
No difference in 3-yr DFS; increased toxicity (n =400)

**PETACC 3** (van Cutsem, ASCO 2005 #LBA8)
Added irinotecan to LV5FU2 in stage II/III patients
No difference in 3-yr DFS without post-hoc statistical analysis (n=3,005)

**CALGB C89803** (Saltz, ASCO 2004 #3500)
Added irinotecan to weekly 5-FU/LV in stage III patients
No difference in 3-yr DFS; increased toxicity (n=1,250)
### Adjuvant Therapy for Resected 1°

#### Toxicity: PETACC-3

<table>
<thead>
<tr>
<th>Side Effect (grade 3/4)</th>
<th>I+F</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>28%</td>
<td>6%</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Neutropenic infection</td>
<td>2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>19%</td>
<td>2%</td>
</tr>
<tr>
<td>60d mortality</td>
<td>0.4%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Van Cutsem, ACSO 2005
Adjuvant Therapy for Resected 1°
PFS: CALGB 89803

Saltz, JCO 2007
Substituting capecitabine for 5-FU/LV

“X-ACT” noninferiority trial

- n = 1,987
- Stage III colon CA
- Primary endpoint: 3-yr disease free survival (DFS)

Bolus 5-FU/LV
- (“Mayo”)
- 6 months

Capecitabine
- 1,250 mg/m² BID

Twelves, NEJM 2005
Adjuvant Therapy for Resected 1°

X-ACT

3 yr Disease-Free Survival:
- Capecitabine 64.2%
- 5-FU/LV 60.6%
  (p=.12)

- The primary endpoint was equivalence of disease-free survival, which was met (HR = .87, p<.001 for equivalence; p=.05 for superiority)
- Reduced toxicity

Twelves, NEJM 2005
## Toxicity: X-ACT

<table>
<thead>
<tr>
<th>Side Effect (grade 3/4)</th>
<th>Capecitabine</th>
<th>5-FU/LV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>2%</td>
<td>26%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11%</td>
<td>13%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Hand-Foot Syndrome</td>
<td>17%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>2%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Greater grade 3/4 toxicities in monthly bolus 5-FU/LV group; QoL scores were similar.

Twelves, NEJM 2005
Adjuvant Therapy for Colon Cancer after Resection of the Primary:

1) For stage III (node-positive) disease, standards include FOLFOX (FLOX can be considered), 5-FU/LV (most use Roswell Park), or capecitabine

2) For stage II disease, there is no “standard”: observation, 5-FU/LV, and FOLFOX can all be considered

3) Irinotecan-based regimens not recommended

4) Most current trials evaluate 2 issues:
   - adding the “biologics” (bevacizumab, cetuximab)
   - substituting capecitabine for infusional 5-FU
## Trials: Adjuvant Therapy for Resected Primary Disease

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP C-08</td>
<td>mFOLFOX6 +/- bevacizumab (12 mos)</td>
</tr>
<tr>
<td>N0147</td>
<td>FOLFOX +/- cetuximab (US Intergroup)</td>
</tr>
<tr>
<td>AVANT</td>
<td>FOLFOX4 vs FOLFOX + bevacizumab vs XELOX + bevacizumab</td>
</tr>
<tr>
<td>QUASAR-2</td>
<td>capecitabine +/- bevacizumab</td>
</tr>
<tr>
<td>MOSAIC-2</td>
<td>FOLFOX +/- bevacizumab vs XELOX + bevacizumab</td>
</tr>
</tbody>
</table>
Colorectal Cancer: Chemotherapy

Outline:

1. Brief background
2. Adjuvant chemotherapy for colon cancer
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4. Metastectomy issues
### Therapy for Advanced Colorectal Cancer: Response rates and survival

<table>
<thead>
<tr>
<th><strong>First Line</strong></th>
<th><strong>Second Line</strong></th>
<th><strong>Third Line</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- FOLFOX or CAPOX or FOLFIRI +/- Bevacizumab</td>
<td>- FOLFOX or FOLIRI or Irinotecan alone Irinotecan/Cetuximab +/- Bevacizumab</td>
<td>- Irinotecan + Cetuximab - Cetuximab Panitumumab</td>
</tr>
</tbody>
</table>

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

**Survival Benefit in Randomized Trials:**
- Yes
- Yes
- Yes
Therapy for Advanced Colorectal Cancer:
Example of starting with oxaliplatin-based therapy

<table>
<thead>
<tr>
<th>First Line</th>
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<th>Third Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>- FOLFOX</td>
<td>- FOLFOX</td>
<td>- Irinotecan + Cetuximab</td>
</tr>
<tr>
<td>- CAPOX</td>
<td>- FOLIRI</td>
<td>- Irinotecan alone or Cetuximab</td>
</tr>
<tr>
<td>- FOLFIRI</td>
<td>{ - Irinotecan alone or</td>
<td>- Cetuximab</td>
</tr>
<tr>
<td></td>
<td>FOLFIRI}</td>
<td></td>
</tr>
<tr>
<td>+/- Bevacizumab</td>
<td>- Irinotecan/Cetuximab</td>
<td>- Panitumumab</td>
</tr>
<tr>
<td></td>
<td>+/- Bevacizumab</td>
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Therapy for Advanced Colorectal Cancer: Example of starting with irinotecan-based therapy

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<td>Irinotecan +</td>
</tr>
<tr>
<td>CAPOX</td>
<td>FOLIRI</td>
<td>Cetuximab</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td></td>
<td>Irinotecan alone or</td>
</tr>
<tr>
<td>+/- Bevacizumab</td>
<td></td>
<td>Cetuximab</td>
</tr>
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<td></td>
<td></td>
<td>Irinotecan/Cetuximab</td>
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<td></td>
<td>Panitumumab</td>
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<tr>
<td></td>
<td></td>
<td>+/- Bevacizumab</td>
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### Colorectal Cancer: Chemotherapy

**Selected Key Trials: Cytotoxics**

<table>
<thead>
<tr>
<th>Study</th>
<th>Bottom Line</th>
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</thead>
<tbody>
<tr>
<td>1) N9741 Trial</td>
<td>FOLFOX is better than IFL or IROX (Goldberg, <em>JCO</em> 2004)</td>
</tr>
<tr>
<td>2) GERCOR</td>
<td>FOLFIRI-FOX is same as reverse (Tournigand, <em>JCO</em> 2004)</td>
</tr>
<tr>
<td>3) NO16966</td>
<td>FOLFOX and CAPOX similar (Cassidy ESMO 2006, Saltz ASCO 2007)</td>
</tr>
<tr>
<td>4) BICC-C</td>
<td>FOLFIRI better than IFL or CAPIRI (Fuchs, <em>JCO</em> 2007)</td>
</tr>
</tbody>
</table>
Studies of Cytotoxics for Advanced Colorectal Cancer Tournigand Trial (GERCOR)

Randomized trial of 220 patients comparing the sequence of FOLFOX and FOLFIRI.

Untreated advanced colorectal cancer (N=220)

Arm A: FOLFIRI -> FOLFOX

Arm B: FOLFOX -> FOLFIRI

First-line therapy continued until progression, at which time the second-line therapy was instituted.
Doesn’t matter whether you start with FOLFOX or FOLFIRI

There are specific reasons why one regimen may be chosen over another for an individual patient.

Fig 4. Overall survival curves. FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX6, folinic acid, fluorouracil, and oxaliplatin.

Tournigand, JCO 2004
Studies of Cytotoxics for Advanced Colorectal Cancer

- Substituting capecitabine for infusional 5-FU
- Adding bevacizumab to oxaliplatin regimens 1st line

**NO16966** (Cassidy, ESMO 2006)

Randomized phase III trial of 2035 patients comparing FOLFOX vs XELOX with or without bevacizumab (Avastin) in first-line colorectal CA

- Previously untreated metastatic colorectal cancer
  - n=2035

- FOLFOX
  - n=317
  - Placebo (n= 350)
  - Bev (n= 350)

- XELOX
  - n=317
  - Placebo (n= 351)
  - Bev (n= 350)

FOLFOX = 5-FU. LV, oxaliplatin
XELOX = capecitabine, oxaliplatin
XELOX and FOLFOX appear equivalent
NO16966 (Cassidy, ESMO 2006)
XELOX and FOLFOX appear equivalent
Porschen, JCO 2006 (Letter)

“True equivalence” of these regimens is highly controversial; differences are unlikely to be clinically significant and often economic factors are raised in discussions.
Studies of Cytotoxics for Advanced Colorectal Cancer
• Adding celecoxib to conventional chemo (no effect)
• FOLFIRI vs CAPIRI vs IFL

Randomized phase III trial of 430 + 117 patients comparing FOLFIRI, mIFL, CAPIRI, initially +/- celecoxib (COX2).

#4 BICC-C Trial

Previously untreated metastatic colorectal cancer
n=430 + 117

“Period 1”

FOLFIRI
n=144

mIFL
n=141

CAPIRI
n=145

“All arms +/- celecoxib

“Period 2”

FOLFIRI/Bev
n=57

mIFL/Bev
n=60

discontinued

Fuchs, JCO 2007
Studies of Cytotoxics for Advanced Colorectal Cancer
BICC-C Trial (Fuchs, JCO 2007): Efficacy

**Period 1**

- FOLFIRI vs mFL
- FOLFIRI vs Capez
- mFL vs Capez

**Period 2**

- FOLFIRI + bevacizumab vs mFL + bevacizumab

Fuchs, JCO 2007
Studies of Cytotoxics for Advanced Colorectal Cancer
BICC-C Trial (Fuchs, JCO 2007): Toxicity

- Period 1: CAPIRI was associated with much higher rates of g3/4 diarrhea, N/V, dehydration, hand-foot syndrome.

- Period 2: FOLFIRI/Bev had higher rates of g3 HTN, neutropenia, N/V
Colorectal Cancer: Chemotherapy

Selected Key Trials: Biologics

1) “Bond” Trial  Cetuximab/Irinotecan better than Cetx alone
(Cunningham, *NEJM* 2004; Saltz, *JCO* 2004)

2) “Hurwitz” Trial  Bevacizumab/IFL better than IFL, 1st line
(Hurwitz, *NEJM* 2004)

3) N016966  Bevacizumab adds to FOLFOX or CAPOX
(Cassidy ESMO 2006, Saltz, ASCO 2007)

3) PACCE  Panitumumab does not add to FOLFOX/Bev
(Hecht, World GI 2007)
“Targeted Therapy”, or “Biologics” in Colorectal Cancer

1) Cetuximab
   (Erbitux™; monoclonal antibody against EGFR)

2) Panitumumab
   (Vectibix™; monoclonal antibody against EGFR)

3) Bevacizumab
   (Avastin™; monoclonal antibody against VEGF)

EGFR = Epidermal Growth Factor Receptor

VEGF = Vascular Endothelial Growth Factor
The HER Family

HER = Human Epidermal growth factor Receptor

growth factor binding sets off a signaling cascade in the cell to stimulate cancer cell growth
Proposed Mechanism of Action of Cetuximab (Erbitux)

ERBITUX package insert, February 2004
Studies of Biologics for Advanced Colorectal Cancer

#1: “Bond” Trial (Cunningham, NEJM 2004)

Randomized phase II trial of 329 patients with irinotecan-refractory disease comparing cetuximab with cetuximab/irinotecan.

**Arm A:** Cetuximab* + irinotecan

**Arm B:** Cetuximab* + PD

Optional crossover to Arm A

**EMR 62202-007**

Irinotecan-refractory advanced CRC

N=329 (randomized 2:1)

EGFR ≥1+ IHC

*400 mg/m² wk 1 (loading), then 250 mg/m² qweek.
Cetuximab With and Without Irinotecan in HER1/EGFR-Positive Irinotecan-Refractory Metastatic Colorectal Cancer: Time to Progression

Note: overall survival curves were nearly identical.

Cunningham, NEJM 2004
Panitumumab: Progression-Free Survival
versus Best Supportive Care

Hazard ratio = 0.54
(95% CI: 0.44, 0.66)

Stratified log-rank test
$p < 0.000000001$

Response Rate = 8% (vs 0%)
Stable Disease = 28% (vs 10%)

Peeters, AACR 2006
Unique side effects:

- Patient on EGFR inhibitor similar to cetuximab or panitumumab

- Also carefully monitor magnesium with EGFR mAb’s

Herbst et al, JCO 2002
Blood Vessels and Tumor Growth

• Solid tumors cannot grow beyond 1 to 2 mm³ without an increase in blood supply via new vessel formation¹
• “Angiogenesis” is thus required for tumor growth and metastasis¹
• Inhibition of tumor angiogenesis leads to tumor cell growth arrest, death of tumor cells, and in some cases, tumor regression²

Tumor angiogenesis is stimulated… New vessels then facilitate tumor growth.

Courtesy of Novartis Oncology
VEGF: A Central Mediator of Angiogenesis

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

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

Binding and activation of VEGF receptor

Endothelial cell activation

ANGIOGENESIS

Survival, Proliferation, Migration

Studies of Biologics for Advanced Colorectal Cancer

#2 Bevacizumab Trial (Hurwitz, NEJM 2004)

Randomized phase III trial of 813 patients comparing chemo with or without bevacizumab (Avastin)

“AVF2107”

Previously untreated metastatic colorectal cancer
N=813

IFL = Irinotecan / 5-FU / Leucovorin

Arm A: IFL + Bevacizumab*

Arm B: IFL + Placebo
Bevacizumab (5 mg/kg q2 weeks) added to IFL significantly improved overall survival by 4.5 months.

Hurwitz, NEJM 2005
Studies of Biologics for Advanced Colorectal Cancer
• Substituting capecitabine for infusional 5-FU
• Adding bevacizumab to oxaliplatin regimens 1st line

#3 NO16966 (Cassidy, ESMO 2006)

Randomized phase III trial of 2035 patients comparing FOLFOX vs XELOX with or without bevacizumab (Avastin) in first-line colorectal CA

Previously untreated metastatic colorectal cancer
n=2035

FOLFOX = 5-FU, LV, oxaliplatin

XELOX = capecitabine, oxaliplatin

FOLFOX n=317

BEV (n=350)

Placebo (n=350)

XELOX n=317

BEV (n=350)

Placebo (n=351)
Survival Advantage for Bevacizumab NO16966 Pooled Analysis (Cassidy, ESMO 2006)

FOLFOX + Placebo/XELOX + Placebo, n=701; 547 events
FOLFOX + Bev/XELOX + Bev, n=699; 513 events

HR=0.83 [97.5% CI 0.72–0.95] (ITT)
P=0.0023

Why were results from NO16966 less impressive? (Cassidy, ESMO 2006)

- In AVF2107 77% of patients received bevacizumab treatment within 4 weeks from PD or deaths vs 46% of patients in NO16966.
- Early bevacizumab discontinuation, largely unrelated to bevacizumab-specific toxicity, occurred at a ~3-fold higher rate in NO16966 compared with AVF2107.

Studies of Biologics for Advanced Colorectal Cancer

#4 PACCE Trial

Randomized phase III trial of 1000 patients comparing chemo/Bev with or without panitumumab (Vectibix)

Previously untreated metastatic colorectal cancer
N=1000

5-FU/Oxali/Bev N=800
5-FU/Irino/Bev N=200

Hecht, World GI 2007
#4 PACCE Trial

Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th># PFS events (%)</th>
<th>Median (95%CI), mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pmab+bev/Ox-CT</td>
<td>206 (50)</td>
<td>9.0 (8.5-10.4)</td>
</tr>
<tr>
<td>Bev/Ox-CT</td>
<td>172 (42)</td>
<td>10.5 (9.7-11.6)</td>
</tr>
</tbody>
</table>

HR= 1.29 (95% CI: 1.05-1.58)

Patients at risk:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Months</th>
<th>N</th>
<th>Months</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pmab+bev/Ox-CT</td>
<td>413</td>
<td>0</td>
<td>267</td>
<td>5</td>
<td>92</td>
</tr>
<tr>
<td>bev/Ox-CT</td>
<td>410</td>
<td>0</td>
<td>298</td>
<td>5</td>
<td>96</td>
</tr>
<tr>
<td>ITT set</td>
<td></td>
<td>10</td>
<td>21</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Hecht, World GI 2007
Therapy for Advanced Colorectal Cancer: CONCLUSIONS

1) Mainstays of therapy are:
   - “conventional chemo”: 5-FU (with leucovorin), capecitabine, irinotecan, oxaliplatin
   
   - “biologics”: bevacizumab, cetuximab, panitumumab

2) Infusional regimens (FOLFOX, FOLFIRI) and capecitabine/oxaliplatin (CAPOX) are standard of care

3) Bevacizumab (Avastin) is FDA-approved for use with first-line and second-line (Bev naïve?) regimens.

4) Cetuximab (Erbitux) and Panitumumab ( Vectibix) are FDA-approved for chemo-resistant disease. Both have single-agent survival benefit. Cetuximab is favored in combination regimens for now.
# New Chemotherapy Strategies

"Stop and Go" = No decrement in Survival

## OPTIMOX1 (n=620): Tournigand, JCO 2006

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX4</td>
<td></td>
</tr>
<tr>
<td>FOLFOX7</td>
<td>5-FU</td>
</tr>
<tr>
<td>FOLFOX7</td>
<td></td>
</tr>
</tbody>
</table>

## OPTIMOX2 (n=202): Maindrault-Goebel, ASCO 2006

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX7</td>
<td>5-FU</td>
</tr>
<tr>
<td>FOLFOX7</td>
<td></td>
</tr>
<tr>
<td>FOLFOX7</td>
<td>Observation</td>
</tr>
<tr>
<td>FOLFOX7</td>
<td>Progression</td>
</tr>
</tbody>
</table>

## GISCAD (n=336): Labianca, ACSO 2006

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI</td>
<td></td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>Break</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>Break</td>
</tr>
</tbody>
</table>
Can we afford this?

Per 2 weeks Rx: $7.5 Billion Dollars in the US!

<table>
<thead>
<tr>
<th>Medication</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU (500 mg/m²)</td>
<td>$9</td>
</tr>
<tr>
<td>Leucovorin (500 mg/m²)</td>
<td>$60</td>
</tr>
<tr>
<td>Capecitabine (2000 mg/m²/day)</td>
<td>$850</td>
</tr>
<tr>
<td>Irinotecan (180 mg/m²)</td>
<td>$2,600</td>
</tr>
<tr>
<td>Oxaliplatin (85 mg/m²)</td>
<td>$2,980</td>
</tr>
<tr>
<td>Bevacizumab (5 mg/kg)</td>
<td>$2,750</td>
</tr>
<tr>
<td>Cetuximab (250 mg/m²)</td>
<td>$5,760</td>
</tr>
</tbody>
</table>

1995: 6 months of 5-FU/LV costs ~$500
2004: 20 months therapy with combinations costs $250,000 (pharmacy alone!)

L. Saltz, ASCO 2004
Colorectal Cancer: Chemotherapy

Outline:

1. Brief background
2. Adjuvant chemotherapy for colon cancer
3. Chemotherapy for advanced colorectal cancer
4. Metastectomy issues
Management of MCRC: An Evolving Treatment Algorithm

Diagnosis of MCRC

- Resectable
  - Neoadjuvant/preoperative therapy
    - Surgery
    - Adjuvant therapy
- Unresectable
  - Borderline/potentially resectable
    - First-line
    - Second-line
    - Third-line
    - Fourth-line
  - Treatment continuum
Liver Metastases in CRC

- Survival directly related to liver metastases resectability
  - 5-y OS = 40%-58% following successful resection\(^1\)
  - As high as 71.5% following solitary resection\(^2\)
- Redefining resectability\(^1,3,4\)
  - **Before** (“what was cut out”)
    - Required limited number of metastases (3 to 4)
  - **Now** (“what is left in”)
    - Number of metastases no longer a decision factor
    - Anticipated negative surgical margins
    - \(\geq30\%\) “future liver remnant”
    - Associated with a near-zero operative mortality rate and long-term survival


OS = overall survival.
What is the rationale for neoadjuvant chemotherapy for liver metastases?

- Make unresectable patients resectable.
- Assess chemo-responsiveness of the disease. Continue / switch post-op chemotherapy
- Assess biology and pace of the disease. If new metastases appear during chemotherapy, the patient will be spared likely a fruitless operation.
- Treat micrometastatic disease to increase cure rate/survival.
- Decrease surgical complications by making surgery technically more feasible.
What are possible downsides to neoadjuvant chemotherapy?

- Tumors may grow and become unresectable
  Does this mean a cure is missed, or would the “bad biology” of such a tumor make resection fruitless?

- Complications of chemotherapy may delay or preclude surgery, or increase risks of surgical complications
  “chemo-liver:” veno-occlusive disease, steatosis, steatohepatitis, bleeding/wound healing

- Patient anxiety

- Complete response may complicate surgery
  Surgeon may not be able to find metastatic sites
## Selected Prospective, Randomized Trials for Adjuvant Therapy For Hepatic Resection

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Rx</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FFCD 9002</strong></td>
<td>167</td>
<td>5-FU/LV vs Observation</td>
<td>?Improved DFS</td>
</tr>
<tr>
<td>(Portier, JCO 2006)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intergroup</strong></td>
<td>109</td>
<td>HAI/IV 5-FU vs Observation</td>
<td>Improved RFS</td>
</tr>
<tr>
<td>(M. Kemeny, JCO 2002)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MSKCC</strong></td>
<td>165</td>
<td>HAI/IV 5-FU vs IV 5-FU</td>
<td>Improved OS</td>
</tr>
<tr>
<td>(N. Kemeny, NEJM 1999)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EORTC 40983</strong></td>
<td>364</td>
<td>FOLFOX vs Observation</td>
<td>?Improved PFS</td>
</tr>
<tr>
<td>(Nordlinger, Lancet 2008)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Peri-Operative FOLFOX for Resectable Hepatic Metastases

EORTC 40983

- n = 364, resectable liver metastases*
- Primary endpoint: disease free survival

FOLFOX4
- 6 cycles (3m)

Surgery
- No chemotherapy

FOLFOX4
- 6 cycles (3m)

*1-4 metastases: 52% one, 26% two, 15% three, 7% four mets
56% colon CA, 42% rectal CA

Nordlinger, Lancet 2008
### Phase 3 Trial of Perioperative FOLFOX4 and Surgery for Resectable CRC Liver Metastases (EORTC 40983): Complications of Surgery

<table>
<thead>
<tr>
<th>Postoperative complications</th>
<th>Perioperative CT</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>40/159 (25.2%(^a))</td>
<td>27/170 (15.9%(^a))</td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary failure</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Biliary fistula</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>(incl output &gt;100 mL/d, &gt;10 d)</td>
<td>(6)</td>
<td>(1)</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>(incl bilirubin &gt;10 mg/dL, &gt;3 d)</td>
<td>(6)</td>
<td>(3)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Intra-abdominal infection</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Need for reoperation</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Incl. postoperative death</td>
<td>1 patient</td>
<td>2 patients</td>
</tr>
</tbody>
</table>

\(^a\)P=0.04.

Nordlinger, Lancet 2008
**Phase 3 Trial of Perioperative FOLFOX4 and Surgery for Resectable CRC Liver Metastases (EORTC 40983): Lesion Size After Preoperative CT**

**Median size of lesions,\(^a\)**  
mm (range)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Before preoperative CT</td>
<td>50 (20-255)</td>
<td></td>
</tr>
<tr>
<td>After preoperative CT</td>
<td>30 (0-230)</td>
<td></td>
</tr>
<tr>
<td>Relative change, %</td>
<td>-26(^b)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Sum of the largest diameters.

\(^b\)Nordlinger, Lancet 2008.
Phase 3 Trial of Perioperative FOLFOX4 and Surgery for Resectable CRC Liver Metastases (EORTC 40983): PFS

- Perioperative CT with FOLFOX4 improved PFS in pts with resectable liver metastases (eligible patients; p=.058 for all)

HR = hazard ratio; CI = confidence interval.

Nordlinger et al, Lancet 2008
Peri-Operative Chemotherapy for Resectable Hepatic Metastases

Follow-Up study:
“BOS” trial: biologics, oxaliplatin, and surgery

**EORTC 40051**

<table>
<thead>
<tr>
<th>n = 100, resectable liver metastases*</th>
<th>FOLFOX6/cetuximab 6 cycles (3m)</th>
<th>Surgery</th>
<th>FOLFOX6/cetuximab + bevacizumab</th>
</tr>
</thead>
</table>

Primary endpoint: disease free survival

Endpoints: response, safety, resection rate, PFS, OS

*”potentially completely resectable; 1-2 lung mets allowed

Adjuvant therapy after resection of primary disease

- Multiple large trials with thousands of patients
- Consistent entry criteria
- Extensive safety/toxicity data
- Long-term follow up
- Modern regimens with widely used drugs

Adjuvant therapy after resection of hepatic metastases

- Few small trials (only 100-350 patients)
- Different entry criteria
- Little safety/toxicity data with long-term follow up
- Older chemotherapy drugs & modalities not in wide use

Should Neoadjuvant or Adjuvant Chemotherapy be Routinely Given?
Should patients who **progress** on neoadjuvant chemotherapy undergo resection? Survival drops off sharply.

<table>
<thead>
<tr>
<th>Group (neoadj chemo)</th>
<th>DFS (5 yrs)</th>
<th>OS (5 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery after response</td>
<td>21%</td>
<td>37%</td>
</tr>
<tr>
<td>Surgery after stable dz</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Surgery after progression</td>
<td>3%</td>
<td>8%</td>
</tr>
</tbody>
</table>

n=131 liver resection patients

**Tumor Progression While on Chemotherapy**

*A Contraindication to Liver Resection for Multiple Colorectal Metastases?*

Overall survival in relation to the response to pre-op chemo

Responders

Progressors

Adam, Ann Surg 2004
## Chemotherapy Liver Toxicity: Selected Reports

<table>
<thead>
<tr>
<th>Report</th>
<th>drugs</th>
<th>toxicity</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubbia-Brandt</td>
<td>5-FU/ Ox</td>
<td>sinusoidal</td>
<td>51% total</td>
</tr>
<tr>
<td>Ann Oncol 2004, n=153</td>
<td>Ox</td>
<td>congestion</td>
<td>78% oxali</td>
</tr>
<tr>
<td>Fernandez</td>
<td>5-FU/ Ox / I</td>
<td>steato-</td>
<td>64% I + O</td>
</tr>
<tr>
<td>J AM C Surg 2005, n=37</td>
<td>Ox / I</td>
<td>hepatitis</td>
<td>10% 5-FU</td>
</tr>
<tr>
<td>Karouii</td>
<td>5-FU/ Ox / I</td>
<td>sinusoidal</td>
<td>49% chemo</td>
</tr>
<tr>
<td>Ann Surg 2006, n=67</td>
<td>Ox / I</td>
<td>dilation</td>
<td>14% no chemo</td>
</tr>
<tr>
<td>Aloia</td>
<td>5-FU Ox</td>
<td>vascular</td>
<td>52% chemo</td>
</tr>
<tr>
<td>JCO 2006, n=75</td>
<td>Ox</td>
<td>changes</td>
<td>18% no chemo</td>
</tr>
</tbody>
</table>

Ox = oxaliplatin; I = Irinotecan
## Chemotherapy Liver Toxicity: Selected Reports

<table>
<thead>
<tr>
<th>Report</th>
<th>toxicity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubbia-Brandt</td>
<td>sinusoidal</td>
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<td>steato-</td>
<td>J AM C Surg 2005, n=37</td>
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<td>Karouli</td>
<td>sinusoidal</td>
<td>Ann Surg 2006, n=67</td>
</tr>
<tr>
<td>Aloia</td>
<td>vascular</td>
<td>JCO 2006, n=75</td>
</tr>
</tbody>
</table>

(vaso-dilation / congestion)
Chemotherapy Liver Toxicity: Selected Reports

Karoui, Ann Surg 2006

Influence of Number of Cycles of Pre-Op Chemo on Morbidity

More is not better!
Special Issues with Bevacizumab

Bevacizumab

VEGF inhibitor with a half-life of 20 days.

In the pivotal phase III trial (Hurwitz), bevacizumab was associated with rare episodes of GI perforation and bleeding, and there have also been reports of impaired wound healing, thrombosis, RPLS.

A subsequent trial (ECOG 3200) showed an acceptable toxicity profile at double the FDA-approved dose (10 mg/kg).

Most experts recommend waiting 6-8 weeks prior, or after, major surgery to avoid peri-operative complications.
## Special Issues with Bevacizumab

**Peri-operative safety of bevacizumab (Avastin)**

### Surgery -> Chemotherapy within 28-60 days

<table>
<thead>
<tr>
<th></th>
<th>IFL</th>
<th>IFL/Avastin</th>
<th>FU/LV/Avastin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scappaticci, ASCO 2004</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=155</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>5 (2.8%)</td>
<td>3 (1.7%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Wound complications</td>
<td>0</td>
<td>3 (1.7%)</td>
<td>0</td>
</tr>
</tbody>
</table>

### Chemotherapy -> Surgery within 60 days

<table>
<thead>
<tr>
<th></th>
<th>IFL</th>
<th>IFL/Avastin</th>
<th>FU/LV/Avastin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hurwitz, ASCO 2004</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding or wound complications</td>
<td>0</td>
<td>4 (10%)</td>
<td>1 (7%)</td>
</tr>
</tbody>
</table>
### Special Issues with Bevacizumab

#### Peri-operative safety of bevacizumab (Avastin)

**Implantation of Venous Access Device (VAD) -> Chemotherapy (including bevacizumab) within 7 days**  
*(message = no need to delay bevacizumab after VAD)*

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Bev within 7d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=330</td>
<td>n=102</td>
</tr>
<tr>
<td>Wound Healing</td>
<td>8 (2.4%)</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Catheter-Related</td>
<td>5 (1.5%)</td>
<td>4 (4.0%)</td>
</tr>
<tr>
<td>thrombosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Berry, “BEAT” Trial, ASCO GI 2006
Adjuvant Chemotherapy Following Hepatic Resection

“it just makes sense”

Yes

No

“there’s little data to support it”

- Adjuvant chemotherapy saves lives in lower-risk patients
- Chemotherapy for advanced disease doubles or quadruples survival compared to nothing
- Appears to be safe
- HAI not needed in era of more effective chemotherapies

- Little data to support routine use
- Optimal drugs, duration, schedules are major unknowns
- Possibly increased complications with widespread use
- Implementation will make clinical trials impossible
If adjuvant chemotherapy is given for patients with resected liver metastases...

“Treat them with adjuvant Rx”

NO “BIOLOGICS”
- No data to support use of biologics in adjuvant setting, possible increased complications, costs.
- Drugs which work in advanced disease may not adjuvantly (e.g., cpt-11)

“Treat with advanced disease regimens”

INCLUDE “BIOLOGICS”
- Patients with liver mets already have “biology” of advanced disease
- Given the high risk of recurrence, why not be as aggressive as possible?
Are we entering a new era in cancer treatment?

**Optimist:** higher response rates, better survival, less side effects than ever before.

**Pessimist:** we are still not curing cancer, the costs are skyrocketing, our money should be going towards prevention and other diseases.

Thank you for your kind attention!