Chemotherapy for metastatic colorectal cancer

UCSF Postgraduate Course in General Surgery
March 22, 2011

Emily Bergsland
UCSF Helen Diller Family Comprehensive Cancer Center

Outline

- Chemotherapy regimens used for metastatic CRC
- Perioperative therapy
  - Resectable
  - Unresectable
- Potential risks of neoadjuvant therapy
- Targeted therapies in the treatment of patients with mCRC
- Does a radiographic CR mean a cure?

Advances in the Treatment of Colorectal Cancer: A moving target!


- Infusional 5-FU regimens and capecitabine are safer and efficacious alternatives to bolus 5-FU (RR 20%)
- FOLFOX = CAPOX (RR 38%, PFS=8 mo, OS 19 mo)
  - Cassidy, et al. JCO, 2008
- FOLFOX and FOLFIRI are both appropriate 1st-line regimens. The specific sequence may be less important than eventual treatment with all three active drugs (5-FU/LV, irinotecan, and oxaliplatin)
  - Oxaliplatin (pt, neuropathy); irinotecan (alopecia, GI toxicity)
    - Tournigand, et al. JCO, 2004
    - Grothey A, et al. JCO, 2005
- Combination therapy associated with 35-45% RR, median OS 18-21 mo (compared to OS 1 yr, RR 15-20% with 5-FU alone)
**Evaluation of FOLFOX6/FOLFIRI Sequence**

<table>
<thead>
<tr>
<th>Previously untreated mCRC (N=220)</th>
<th>FOLFIRI (n=109)</th>
<th>FOLFOX6 (n=81)</th>
<th>FOLFOX6 (n=111)</th>
<th>FOLFIRI (n=69)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR %</td>
<td>56*</td>
<td>15†</td>
<td>54*</td>
<td>4†</td>
<td>0.68</td>
</tr>
<tr>
<td>Median PFS (mo)</td>
<td>14.2</td>
<td>10.9</td>
<td>21.5</td>
<td>20.6</td>
<td>0.99</td>
</tr>
</tbody>
</table>

- FOLFIRI: more grade 3/4 mucositis, grade 2 alopecia
- FOLFOX6: more grade 3/4 neutropenia, neurosensory toxicity

*By stratified log-rank test.†By chi-square test.

Targeted therapies in mCRC:

- Bevacizumab (anti-VEGF MAb)
- Panitumumab & Cetuximab (anti-EGFR MAb)

**FOLFOXIRI More Effective Than FOLFIRI in patients w/ unresectable mCRC**


- Overall response rate significantly higher with FOLFOXIRI—60% vs 34% with FOLFIRI (P=0.0002)—external review (1° EP)
- OS and PFS longer with FOLFOXIRI—Median PFS, 9.8 vs 6.9 months; P<0.0001
  - Median OS 22.6 mo vs 16.7 mo; p=0.032
- FOLFOXIRI associated higher grade ¾ toxicity—Gr 2/3 Neurotoxicity (0 vs 19%), gr ¾ neutropenia (28 vs 50%)—both p<0.001
- R0 liver resection rate: 15% vs 6%, p=0.033 (36% vs 12% in pt with liver-only, p=0.017)

**Phase III trial 1st line chemo+/- bev for mCRC: Efficacy**

<table>
<thead>
<tr>
<th></th>
<th>Placebo + IFL (n=411)</th>
<th>Bevacizumab + IFL (n=402)</th>
<th>P Value</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>15.6</td>
<td>20.3</td>
<td>&lt;0.001*</td>
<td>0.66</td>
</tr>
<tr>
<td>PFS (months)</td>
<td>6.2</td>
<td>10.6</td>
<td>&lt;0.001*</td>
<td>0.54</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>35</td>
<td>45</td>
<td>&lt;0.01†</td>
<td></td>
</tr>
<tr>
<td>DOR (months)</td>
<td>7.1</td>
<td>10.4</td>
<td>0.001*</td>
<td>0.62</td>
</tr>
</tbody>
</table>

*By stratified log-rank test.†By chi-square test.

Conclusions

• First phase III validation of an anti-angiogenesis strategy to treat human cancer

• Approved by the FDA in 2004 for first-line treatment of patients with mCRC (in combination with 5-FU-based chemotherapy)
  – Use in combination with FOLFOX, CAPOX, FOLFIRI, or 5-FU/LV

• Weigh benefits vs risks (e.g. perforation, ATE, HTN, proteinuria, wound healing)

Bevacizumab in First-Line MCRC: Grade 3/4 Wound Healing and Bleeding Complications

<table>
<thead>
<tr>
<th>No. of Patients (%)</th>
<th>Chemotherapy + Placebo</th>
<th>Chemotherapy + Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery 28-60 days prior to therapy</td>
<td>1/194 (0.5)</td>
<td>3/230 (1.3)</td>
</tr>
<tr>
<td>Surgery during therapy</td>
<td>1/29 (3.4)</td>
<td>10/75 (13.3)</td>
</tr>
</tbody>
</table>

Hold BEV for 6-8 wk (2-3 x T1/2) prior to elective surgery: T1/2 17-21 days


NO16966: XELOX +/- Bevacizumab vs FOLFOX4 +/- Bevacizumab

Initial 2-arm Randomization

Amended 2x2 Design Based on Bevacizumab Phase III Data

Bevacizumab Improves PFS But Not ORR When Added to Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX or XELOX + Placebo (n=699)</th>
<th>FOLFOX or XELOX + Bevacizumab (n=701)</th>
<th>HR (97.5% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, (mo)</td>
<td>9.4</td>
<td>8.0</td>
<td>0.83 (0.72-0.95)</td>
<td>0.002</td>
</tr>
<tr>
<td>Median TTP, (mo)</td>
<td>6.9</td>
<td>6.0</td>
<td>0.84 (0.74-0.96)</td>
<td>0.003</td>
</tr>
<tr>
<td>Median OS, (mo)</td>
<td>21.3</td>
<td>19.9</td>
<td>0.89 (0.76-1.03)</td>
<td>0.0769</td>
</tr>
<tr>
<td>ORR*, %</td>
<td>38%</td>
<td>38%</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

PFS, progression-free survival; TTP, time to progression; OS, overall survival; ORR, overall response rate; HR, hazard ratio; CI, confidence interval.

*Independent review

Saltz L, et al. JCO, 2008
Summary: Bevacizumab and chemotherapy for mCRC

- First-line setting:
  - BEV enhance activity of IFL, 5 mo increase OS vs 5-FU
  - Incremental benefit of BEV added to XELOX or FOLFOX is modest (1 mo TTP, no diff OS or RR)
  - Utility of BEV + FOLFIRI has not been established
- BEV enhances activity of FOLFOX in 2nd line setting (2x RR, 2.5 mo increase in PFS, 2 mo increase OS)
- Utility of continued treatment past progression is unknown
- Additional studies ongoing

Status of FDA-Approved EGFR Inhibitors in mCRC

- Panitumumab (Vectibix)
  - Refractory disease, monotherapy
  - 10% RR
- Cetuximab (Erbitux)
  - Irinotecan-resistant or refractory dz, +/- irinotecan (11% RR with cetux, 23% cetux/irino)
- Class-related toxicity
  - Hypomagnesemia, rash, paronychia, infusion rxns

EGFR Activation Mediates Several Processes

Predictors of response to cetuximab

- Response to cetuximab does not correlate with EGFR expression by IHC; same response rate in EGFR (-) tumors
  - Chung, et al. JCO, 2005;23:1803-1810
- Intensity of rash correlates with activity
- Presence of a KRAS (codon 12/13) mutation in the tumor (≈35-40% pt) predicts for resistance to EGFR inhibitor
  - KRAS p.G13D mutations may retain cetuximab sensitivity
  - De Roock, et al. JAMA, 2010
- Presence of BRAF V600 mutation (present in ≈15% of pt with WT RAS) predicts for resistance to EGFR inhibitor (also prognostic)
EGFR antibodies are active in first-line treatment of mCRC

OPUS Trial: Phase II 1st line FOLFOX+/-cetuximab in mCRC (N=337)
- KRAS wild-type tumors: addition of cetuximab to FOLFOX resulted in improvement in:
  - Response Rate (61% vs. 37%; p=0.011)
  - PFS 7.7 vs 7.2 mo (HR-0.57; p=0.0163)
- In patients with KRAS mutant tumors, the addition of cetuximab to FOLFOX had no apparent benefit
- The safety profiles of cetuximab and chemotherapy were generally comparable and consistent with their known safety profiles


CRYSTAL trial: Phase III 1st line FOLFIRI+/-Cetuximab in mCRC (N=1198)
- Adding cetuximab to FOLFIRI in mCRC leads to a significant PFS (HR=0.85; p=0.048)-1° EP, 8.9 vs 8.0 mo (no diff OS)
- The benefit of cetuximab + FOLFIRI is greater KRAS WT tumors (64% pt):
  - PFS (HR=0.68; p=0.02), 9.9 vs 8.7 mo
  - Response rate 59% vs. 43% (p=0.0025)
- KRAS mutant tumors do not benefit from the combination of cetuximab and FOLFIRI
- The grade ¾ adverse event profile was similar in the KRAS wild-type and mutant populations


First-line treatment with triple combination (chemo + bevacizumab+ EGFR inhibitor) NOT indicated
- PACCE1):
  - Addition of panitumumab to bevacizumab and oxaliplatin- or irinotecan-based chemotherapy ↑toxicity and ↓PFS
  - w/ FOLFOX: ↑grade 3 diarrhea, dehydration and infection; 2x PE (one fatal PE on panitumumab arm)
  - toxicity w/o improved efficacy in combination with FOLFIRI
- CAIRO-22:
  - The addition of cetuximab to CAPOX+ BEV results in a significantly ↓PFS, and ↓QOL (even if KRAS-WT)
  - The addition of cetuximab to CAPOX/BEV results in ↑skin toxicity and diarrhea
  - In patients with KRAS mutation the addition of cetuximab to chemotherapy and bevacizumab results in a significant decrease in PFS


Liver metastases

- Despite advances in systemic tx, 5 yr OS is only 10% and surgery remains only curative option in pt with liver mets
- Liver mets in 25% of pt at Dx, 50-70% at 3 yr
- Initially resectable liver mets in 13-25%
- Pathologic CR with chemotherapy in up to 10%
- Initially unresectable mets can be converted to “resectable” in 10-40%
- Recurrence post-hepatectomy in up to 80%
- Despite this, 5 yr OS post-hepatectomy 37-58%


Colorectal cancer

Liver metastases

Resectable

20%

Survival > 30+% at 5 years

Prior adjuvant studies limited:
Did not complete accrual thus limiting power and/or
Did not assess systemic (modern) chemotherapy

EORTC: Perioperative chemotherapy in resectable liver metastases

Randomize

FOLFOX4 → Surgery → FOLFOX4

6 cycles (3 months)

N=364 patients, up to 4 liver mets
(52% 1, 26% 2, 22% 4)

1° EP PFS @ 3 yr


EORTC 40983 : Conclusions

- Perioperative chemotherapy with FOLFOX is feasible and ↑ PFS in eligible and resected patients (med PFS= 11.7 vs 18.7 mo; p=0.025, HR 0.76)
- Reversible postoperative complications (e.g. infection, fistula, high bili) more common after chemotherapy than up-front surgery
  - Risks of chemotherapy outweighed by benefits
  - Operative mortality <1% in both groups
- PD was seen during preoperative chemotherapy in 7%
  - Biological marker of poor prognosis?
- Relative contribution of adjuvant vs neoadjuvant tx unknown
- 75% of pt had 1-2 mets; applicability if larger burden?

Neoadjuvant Chemotherapy for Resectable Disease: Unresolved Questions

- What are the risks / benefits? Neoadj vs adjuvant?
- FOLFOX or FOLFIRI: does it matter?  → FOLFOXIRI?
- Can we improve outcomes with biologics?
- Optimal candidates/risk stratification?
  → Resectable disease? 1 met = multiple?
    - Post-operative chemo (but not preop) \( \uparrow \) DFS and OS in pt with solitary, metachronous CRLM>5 cm
      - Adam et al. Annals Surgery 2010 (1400 pt, retrospective)
    - Molecular markers?

Liver Toxicity of Neoadjuvant Therapy

- Numerous studies have suggested that neoadjuvant therapy induces many changes, including
  → Increased vascular changes
  → Bluish discoloration, edema, and a spongiform consistency similar to that seen with early cirrhosis, which increases the potential for operative bleeding and decreases hepatic functional reserve
  → Steatohepatitis
  → Hepatic sinusoidal abnormalities similar to those of veno-occlusive disease
  → Disruption of sinusoidal membrane and collagenization of the perisinusoidal space

- Conflicting data limits our ability to draw firm conclusions, but limiting #cycles preop may ↓ post-op complications
  

Liver Toxicity of Neoadjuvant Therapy: Implications

<table>
<thead>
<tr>
<th>Regimen (N)</th>
<th>Sinusoidal Dilation</th>
<th>Steatosis &gt;30%</th>
<th>Steatohepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes % (P)</td>
<td>Yes % (P)</td>
<td>Yes % (P)</td>
</tr>
<tr>
<td>No chemotherapy (158)</td>
<td>1.9 98.1 (NS)</td>
<td>8.9 91.1 (NS)</td>
<td>4.4 95.6 (NS)</td>
</tr>
<tr>
<td>5-FU/LV (63)</td>
<td>0 100 (NS)</td>
<td>16.6 83.4 (NS)</td>
<td>4.8 95.2 (NS)</td>
</tr>
<tr>
<td>5-FU/LV + irinotecan (84)</td>
<td>4.3 95.7 (NS)</td>
<td>10.6 89.4 (NS)</td>
<td>20.2 79.8 (0.0001)</td>
</tr>
<tr>
<td>5-FU/LV + oxaliplatin (79)</td>
<td>18.9 81.1 (0.0001)</td>
<td>3.8 96.2 (NS)</td>
<td>6.3 93.6 (NS)</td>
</tr>
<tr>
<td>Other (12)</td>
<td>0 100 (NS)</td>
<td>8.3 91.7 (NS)</td>
<td>0 100 (NS)</td>
</tr>
</tbody>
</table>

*Comparison of each group vs no chemotherapy.

Chemo-Induced Hepatotoxicity

- Steatosis
- Steatohepatitis
- Veno occlusive changes
- Fibrosis
- Likely related to duration of chemo?
- Type of chemo?

Early Evaluation For Resection

Rubbia-Brandt et al. Annals of Oncol 2004
Neoadjuvant Chemotherapy: Pros & Cons

**PROS**
- Downsize tumor/Convert unresectable to resectable
- Evaluate chemo-responsiveness
- Treat extra-hepatic micromets
- Better chemotolerance pre-op?
- Assess tumor biology (i.e. identify pt who should not go to surgery)

**CONS**
- Miss window of opportunity —early PD precludes surgery
- Delay potentially curative surgery if complications
- Chemotherapy-associated liver damage; morbidity /mortality of surgery
- Radiographic CR could compromise ability to do complete resection


Complete Response to Chemotherapy Does Not Necessarily Mean Cure

- 586 pts treated with chemotherapy between 1998-2004
- 38 pt radiographic CR (at least one lesion) by preop CT and U/S and <10 mets at baseline = 66 mets
- IOUS performed
  - Disappearance of initially resectable site—resected anyway (15)
    - 12/15 viable cancer cells at path
    - Disappearance of initially unresectable site—left in place (31)
    - 23/31 recurred within 1 yr

- Overall, 83% of mets with CR on imaging were found to have persistent macroscopic or microscopic residual disease or early recurrence in situ (<1 yr)

Benoist et al. JCO, 2006

- 435 pt (MSKCC); 39 (9%) had radiologic CR: 68 “lesions” resected; 50 followed for at least 1 yr—38% recurrence rate in CR sites (and 65% recurred overall)

Auer et al. Cancer, 2010

Rescue surgery for unresectable mCRC to liver

Summary: Systemic Therapy for Liver Metastases

- Consider neoadjuvant therapy for resectable disease
  - Relative benefit of adjuvant vs neoadjuvant?
  - Risk of hepatotoxicity?
  - Optimal regimen? (max RR?)
  - Role of biologics?
  - Biological test?
  - Short course (CT after 4-6 cycles)

- Hold bevacizumab 6-8 wk before resection

- In patients with initially unresectable disease— reconsider resection after up-front chemotherapy
  - Consider up-front EGFR inhibitor in borderline resectable Ras WT tumors?
  - Increased toxicity may be warranted to achieve max RR/R0 resection

- Involve the surgeon early!
- Individualize therapy! (RAS mutation, BRAF? PTEN loss? PI3K mutation?)

Response/resection after chemotherapy:

<table>
<thead>
<tr>
<th>REF</th>
<th>Treatments</th>
<th>RR</th>
<th>R0 resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Touringand et al. 2004</td>
<td>FOLFOX</td>
<td>54%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>FOLFIRI</td>
<td>56%</td>
<td>7%</td>
</tr>
<tr>
<td>Falcone, et al. 2007</td>
<td>FOLFIRI</td>
<td>34%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>FOLFOXRI</td>
<td>60% (p=0.0002)</td>
<td>15% (p=0.033)</td>
</tr>
<tr>
<td>Van Cutsem, et al. 2009 WT-Ras subgroup, N=348</td>
<td>FOLFIRI</td>
<td>43%</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>FOLFOXRI/Cetux</td>
<td>59%</td>
<td>?</td>
</tr>
<tr>
<td>Bokemeyer, et al. 2009 WT Ras subgroup, N=134</td>
<td>FOLFOX</td>
<td>37%</td>
<td>4.1%</td>
</tr>
<tr>
<td></td>
<td>FOLFOX/cetux</td>
<td>61% (p=0.011)</td>
<td>9.8%</td>
</tr>
<tr>
<td>Okines, 2009 and Saltz, 2008</td>
<td>XELOX or FOLFOX</td>
<td>38%</td>
<td>4.9%</td>
</tr>
<tr>
<td></td>
<td>XELOX or FOLFOX + BEV</td>
<td>38%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Folprecht et al. 2009 N=111 (CELIM)</td>
<td>FOLFOX/cetux</td>
<td>68%</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td>FOLFIRI cetux</td>
<td>57%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Ongoing phase III studies: resectable disease

<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adj.</td>
<td>284</td>
<td>FOLFOX4 x12 vs FOLFOX7 x6+ FOLFIRIx6</td>
</tr>
<tr>
<td></td>
<td>340</td>
<td>FOLFOX x6 or XELOXx4 +/- Cetuximab (pre/post-op)</td>
</tr>
<tr>
<td>Adj. + Adj.</td>
<td>500</td>
<td>XELOX +/- bevacizumab</td>
</tr>
<tr>
<td>periop pending</td>
<td>Adjuvant FOLFOX/cetux +/- neoadjuvant tx</td>
<td></td>
</tr>
</tbody>
</table>

mCRC | (Folfox or folfiri)+ BEV OR cetuximab (WT-RAS only) | Calgb 80705 |
Personalized cancer medicine: genetic profiling of tumors