Treatment of Advanced Colorectal Cancer

Alexis D. Leal, M.D.
Assistant Professor, GI Medical Oncology
University of Colorado Cancer Center

Disclosures
• None

Objectives
• Review the basics of advanced colorectal cancer
• Review treatment and management of resectable and unresectable colorectal cancer
• Review future directions in the treatment of advanced colorectal cancer
Colorectal Cancer 101:

History and Physical Examination

- Hematochezia – 58%
- Abdominal Pain – 52%
- Unexplained Iron Deficiency Anemia – 57%
- Weight Loss – 39%
- Altered Stools – 25%
- Obstruction – 4%
Diagnosis/Staging

- Labs
  - CBC, CMP, CEA
- Procedures
  - Colonoscopy with biopsy
  - Flexible sigmoidoscopy with biopsy
- Radiology
  - CT scan
  - Chest/Abdomen/Pelvis (Chiest is controversial)
  - PET/CT (?)
  - Liver MRI (?)

Prevalence & Survival by Stage

Factors Influencing Treatment Selection

- Tumor
  - Resectability
  - Biology
  - Symptoms
- Patient
  - Age
  - General Health
  - Other Diseases
  - Preference
- Treatment
  - Efficacy
  - Toxicity
  - Availability
Colorectal Cancer:  
Management of early-stage disease

Limited Stage Colon Cancer

- Stage I through III Colon Cancer (no distant metastases)  
  - Surgical resection first
- Adjuvant Chemotherapy – 3-6 months of chemotherapy  
  - High-Risk stage II
    - Poorly differentiated, T4 tumor, Obstruction/Perforation, Vascular invasion, < 12 Lymph Nodes removed
    - Stage III (any lymph node involvement)
  - FOLFOX (5-fluorouracil and oxaliplatin)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen(s)</th>
<th>Stage III Colon Cancer Patients</th>
<th>Enrolling Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOSCA</td>
<td>CAPOX or FOLFOX4</td>
<td>2462</td>
<td>Italy</td>
</tr>
<tr>
<td>SCOT</td>
<td>CAPOX or mFOLFOX6</td>
<td>3983</td>
<td>UK, Denmark, Spain, Australia, Sweden, New Zealand</td>
</tr>
<tr>
<td>IDEA France</td>
<td>CAPOX or mFOLFOX6</td>
<td>2010</td>
<td>France</td>
</tr>
<tr>
<td>CD0702</td>
<td>mFOLFOX6</td>
<td>2440</td>
<td>US, Canada</td>
</tr>
<tr>
<td>HDRQ</td>
<td>CAPOX or FOLFOX4</td>
<td>708</td>
<td>Greece</td>
</tr>
<tr>
<td>ACHIEVE</td>
<td>CAPOX or mFOLFOX6</td>
<td>1291</td>
<td>Japan</td>
</tr>
</tbody>
</table>

Only large 1 randomized patients have included in the pooled primary analysis.
IDEA Collaboration

Primary DFS Analysis (miTT)

DFS HR = 1.07
95% CI, 1.00 to 1.15

DFS Comparison by Risk Group & Regimen

IDEA Clinical Consensus: Risk based approach to adjuvant therapy for stage III Colon cancer

Risk group
Recommended duration of adjuvant therapy
T1-3 N1
3 months 6 months
(-60% of stage III)
T4 and/or N2 (or other high-risk factors)
Duration of therapy determined by:
- tolerability of therapy
- patient preferences
- assessment of risk of recurrence
- Regional (LAPCOS vs EUROCOS)
Limited Stage Rectal Cancer

- Stage I
  - Surgical Resection First
- Stage II or higher
  - “Neoadjuvant” chemotherapy and radiation (chemoXRT)
  - 5-FU/leucovorin or capecitabine combined with radiation therapy (5 weeks)

Colorectal Cancer:
Management of advanced disease

Resectable
- Oligometastatic disease
  - Resectable metastases in liver or lung
  - Potentially curable with multi-disciplinary approach
  - Surgery +/- adjuvant chemotherapy
  - Neoadjuvant chemotherapy +/- surgery

Unresectable
- Multi-agent chemotherapy +/- biologics
- Clinical trials
- Radiation therapy
- Interventional radiology
  - Radiofrequency ablation (RFA)
  - Embolization
  - Chemoembolization
  - Y90
Surgical Resection of Liver Tumors

Radiation Therapy

- Used prior to surgery or sometimes to treat metastases
- High frequency alternating current
- Heat generation
- protein denaturation
- thermal coagulation
- tissue desiccation

Radiofrequency Ablation (RFA)

- Used either in conjunction with surgery or alone to treat metastases
- High frequency alternating current
- heat generation
- 45°C protein denaturation
- 70°C thermal coagulation
- 100°C tissue desiccation
mCRC Outcomes Have Improved With the Evolution of Treatment Options


<table>
<thead>
<tr>
<th>Median OS Months</th>
<th>1980s</th>
<th>1990s</th>
<th>2000s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>15</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>BSC</td>
<td>10</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>5-FU</td>
<td>10</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>5-FU/LV</td>
<td>6</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

14 FDA Approved Drugs for Colorectal Cancer

<table>
<thead>
<tr>
<th>&quot;Cytotoxics&quot;</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 5-fluorouracil</td>
<td>pyrimidine analog</td>
</tr>
<tr>
<td>2. capcitabine</td>
<td>pyrimidine prodrug</td>
</tr>
<tr>
<td>3. TAS-102</td>
<td>pyrimidine drug with metabolism inhibitor</td>
</tr>
<tr>
<td>4. irinotecan</td>
<td>topoisomerase I inhibitor</td>
</tr>
<tr>
<td>5. oxaliplatin</td>
<td>3rd generation platinum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>&quot;Biologics/Targeted&quot;</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. cetuximab</td>
<td>antibody against EGFR</td>
</tr>
<tr>
<td>2. panitumumab</td>
<td>antibody against EGFR</td>
</tr>
<tr>
<td>3. bevacizumab</td>
<td>antibody against VEGF</td>
</tr>
<tr>
<td>4. ziv-aflibercept</td>
<td>VEGF trap</td>
</tr>
<tr>
<td>5. ramucirumab</td>
<td>antibody against VEGFR2</td>
</tr>
<tr>
<td>6. regorafenib</td>
<td>tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>7. ramucirumab</td>
<td>antibody against VEGFR2</td>
</tr>
<tr>
<td>8. pembrolizumab/nivolumab</td>
<td>antibody against PD-1 (MSI-high only)</td>
</tr>
</tbody>
</table>

Colorectal Cancer is Expensive

- 5-FU (500 mg/m²) $6
- Leucovorin (500 mg/m²) $85
- Captoprilin (200 mg/m²/week) $2,250
- Infusion (150 mg/m²) / generic $2,300 / $480
- Oxaliplatin (85 mg/m²) / generic $4,190 / $590
- Bevacizumab (5 mg/kg) $2,560
- Bevacizumab (5 mg/kg) $2,560
- Cetuximab (250 mg/m²) $5,120
- Oxaliplatin (85 mg/m²) / generic $4,190 / $590
- Infusion (150 mg/m²) / generic $2,300 / $480
- Pembrolizumab (4 mg/kg) $5,900
- Regorafenib (160 mg, 513) $7,139

1997: 6 months of 5-FU/LV costs ~$500  
2017: 30 months of therapy with combinations costs ~$400,000
Overview of EGFR and VEGFR Growth Signaling Pathways

Tumor Cell

Endothelial Cell

Targeted by cetuximab and panitumumab
Targeted by bevacizumab and aflibercept
Targeted by ramucirumab

ONCOGENESIS
ANGIOGENESIS
TUMOR MICROENVIRONMENT


* AFLibercept also targets PIGF

EGFR = epidermal growth factor receptor
PDGFR = platelet-derived growth factor receptor
VEGFR = vascular endothelial growth factor receptor

KRAS Mutations Predict (Lack of) Benefit to EGFR Therapy

KRAS Mutations

Distribution of Mutations in mCRC

New RAS mt ~10%
KRAS mt ~40%
RAS wt ~50%
"PRIME" Trial: KRAS, Atypical KRAS, NRAS

<table>
<thead>
<tr>
<th>Sample</th>
<th>KRAS</th>
<th>NRAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>NRAS</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Both</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

BRAF

- BRAF<sup>wt</sup> present in ~ 7% of metastatic CRC
  - Results in constitutive activation of MAPK signaling
  - Associated with aggressive biology, shorter OS, limited response to chemotherapy
- Associated with:
  - High-risk tumors
  - High grade
  - Older age
  - Female
  - MSS tumors
  - Serrated (as opposed to tubular adenoma pathway)
- BRAF and KRAS mutations appear to be mutually exclusive
BRAF mutation is a negative prognostic factor.

**“CRYSTAL” Trial: 1st Line FOLFIRI/Cetuximab**

- BRAF+ patients: 293
- BRAF- patients: 337

**Right vs. Left Colon Cancer (Sidedness)**

- **Right**: N = 293 (27%)
- **Left**: N = 732 (68%)

**Analysis of CALGB/SWOG 80405**

- Patients with right-sided colon cancer did not benefit from treatment with EGFR inhibitor – even if RAS wild-type.
Current Cancer Treatment Strategy:
One-size-fits-all

Future Directions in Treatment of Colorectal Cancer

BRAF inhibition in Melanoma
BRAF Inhibition in Melanoma

Minimal Efficacy with BRAF or Dual BRAF + MEK Inhibition

- Vemurafenib: 12% Response Rate
- GSK212 + GSK436: 12% Response Rate
A key finding: Feedback EGFR signaling after BRAF inhibition

Mao et al CCR '12, Prahallad et al Nature '12

SWOG S1406: Randomized trial of irinotecan/cetuximab with or without vemurafenib in BRAF-mutant metastatic CRC

Presented at ASCO 2017 by Scott Kopetz, MD, PhD

SWOG S1406: Randomized trial of irinotecan/cetuximab with or without vemurafenib in BRAF-mutant metastatic CRC

Primary Endpoint: Progression-free survival

hazard ratio: 0.48
95% CI: 0.31 - 0.78

Presented at ASCO 2017 by Scott Kopetz, MD, PhD
**SWOG S1406: Randomized trial of irinotecan/cetuximab with or without vemurafenib in BRAF-mutant metastatic CRC**

Presented at ASCO 2017 by Scott Kopetz, MD, PhD

Cancer signaling is complex!


Advances in Understanding the Genetic Landscape of Cancer

- On average, there are ~70 genes mutated per cancer
- However, < 20 pathways will actually drive cancer development
- Most mutations are harmless

Microsatellite High Colorectal Cancer

- Germline (Hereditary):
  - "HNPCC" or Lynch Syndrome
  - Due to mutations in one of the mismatch repair (MMR) genes
    - MLH1, MSH2, MSH6, PMS2, and/or EPCAM
  - Increased lifetime risk of colorectal, endometrial, stomach, ovarian, urothelial, and other cancers.

- Acquired MSI
  - Most due to hypermethylation of the MLH1 promoter and epigenetic silencing of MLH1
  - Can also have "double somatic" MSI caused by mutations in MMR genes.

- Two methods for testing
  - PCR - identify variation in genomic repeats
  - IHC - loss of expression of one or more MMR proteins.

MSI-high tumors have more mutations

Mutations per tumor

- Mismatch repair proficient colon cancers
- Mismatch repair deficient colon cancers
- Normal colon tissue
- Mismatch repair proficient tumors
- Mismatch repair deficient tumors
MSI-high Cancers Have Tumor Infiltrating T-cells (which can help kill cancer)

Redston M. Mod Pathol 2001;14(3).

MSI-H in Colon Cancer: Prevalence and Prognosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Prevalence</th>
<th>Prognosis Compared to MSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>15%-20%</td>
<td>excellent</td>
</tr>
<tr>
<td>III</td>
<td>8%-10%</td>
<td>same</td>
</tr>
<tr>
<td>IV</td>
<td>4%-5%</td>
<td>same or worse</td>
</tr>
</tbody>
</table>

- Hypermutated cancers too "deranged" to metastasize
- Immune system can prevent spread
- But once a metastatic clone has been selected, same or worse prognosis than microsatellite stable CRC

MSI-H, high levels of microsatellite instability; MSS, microsatellite stable.


Presented by Dung Le at 2015 ASCO Annual Meeting
PD-1 and PD-L1 Function as Immune Checkpoints: Prevents Activation


Study Design

<table>
<thead>
<tr>
<th>Colorectal Cancers</th>
<th>Non-Colorectal Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal A Deficient in Mismatch Repair (n=28)</td>
<td>Colorectal B Proficient in Mismatch Repair (n=28)</td>
</tr>
<tr>
<td>Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks</td>
<td>Primary endpoint: immune-related 20-week PFS rate and response rate</td>
</tr>
</tbody>
</table>

Objective Responses

<table>
<thead>
<tr>
<th></th>
<th>MMWR-deficient CRC</th>
<th>MMWR-proficient CRC</th>
<th>MMWR-deficient non-CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>13</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Objective Response Rate</td>
<td>62%</td>
<td>0%</td>
<td>60%</td>
</tr>
<tr>
<td>Disease Control Rate</td>
<td>92%</td>
<td>16%</td>
<td>70%</td>
</tr>
</tbody>
</table>
Responses in MSI-high CRC

A. Biochemical Response

- Monarch-specific colorectal cancer
- Monarch-specific defuse colorectal cancer
- Monarch-specific defuse colorectal cancer

B. Radiographic Response

- 20% increase (progressive disease)
- 20% decrease (partial response)


FDA grants accelerated approval to pembrolizumab for first tissue site agnostic indication

On May 12, 2015, the U.S. Food and Drug Administration (FDA) granted accelerated approval to pembrolizumab (Keytruda; Merck & Co., Inc.), a humanized monoclonal antibody, for the treatment of patients with recurrent, progressive, or metastatic microsatellite instability-high colorectal cancer who have progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. Pembrolizumab is intended for patients with tumors that have microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancer as determined by an FDA-approved assay.

The approval is based on an increase in overall survival in patients with MSI-H colorectal cancer who have progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. Pembrolizumab is indicated in combination with fluoropyrimidine, oxaliplatin, and irinotecan for the treatment of patients with MSI-H colorectal cancer who have progressed following fluoropyrimidine, oxaliplatin, and irinotecan (FOLFOXIRI) and with fluoropyrimidine, oxaliplatin, and irinotecan (FOLFIRINOX) for patients who have not progressed following FOLFIRINOX.
Treatment of Colorectal Cancer

- The revolution of genetic information on tumors over the last 5 years has greatly increased understanding of tumor biology
- But... this has not yet translated into the clinic, since surgery is still the mainstay of curing solid tumors like colorectal cancer
- Ignorance (lack of research) is costly and deadly: without knowledge of KRAS/NRAS, for instance, we would be spending ~$800,000,000 per year harming patients
- Knowledge of relevant biomarkers is critical in curing colorectal cancer patients; however, important to use markers that have been validated/qualified across multiple studies

Take Home Points

- Some patients with metastatic CRC can be cured with multidisciplinary approach
- RAS mutations predict lack of benefit to EGFR inhibitors
- BRAF mutations signify more aggressive cancer BUT clinical trials show promising treatment options
- Metastatic/unresectable MSI-H CRC may benefit from immunotherapy
  - Clinical trial open at UCD – 1st line chemo vs. pembrolizumab
- Consider clinical trial options for patients with metastatic disease and good PS

Thank you!!

Alexis.Leal@ucdenver.edu