Molecular Diagnostics and Targeted Therapeutics in the Management of Colorectal Cancer

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Overview

- Personalized Medicine in CRC: definitions
- Incorporating Molecular Diagnostics and Targeted Therapeutics into Current Management Strategies for CRC
  - Multidisciplinary Treatment by Stage
    - Surgery
    - Molecular prognostic features
    - Chemotherapeutic & Biologic Agents
Case Presentation #1 (Audience Response)

- 74 year male with stage IIA (T3N0M0) sigmoid colon adenocarcinoma status post laparoscopic sigmoid colectomy 30 days ago.

- Under which circumstance can additional testing be considered (12-gene signature assay) prior to recommending adjuvant chemotherapy?

A. No high risk features + MSI-high
B. 1 high risk feature + MSI-high
C. No high risk features + MSS
D. 1 high risk feature + MSS
E. None of the above
Prognostic vs. Predictive Biomarkers

- **Prognostic:**
  - A biomarker that informs outcome among patients, regardless of treatment rendered

- **Predictive:**
  - A biomarker that informs benefit (or harm) from a particular treatment
Colorectal Carcinogenesis

A Genetic Model for Colorectal Tumorigenesis

Eric R. Fearon and Bert Vogelstein
The Oncology Center
Program in Human Genetics
The Johns Hopkins University School of Medicine
Baltimore, Maryland 21231

Polyacrylamide gel image and electropherograms for a hereditary nonpolyposis colorectal cancer tumor paired with normal tissue.
Surgery: considerations

- High Risk Features
  - Grade 3 or 4
  - Lymphovascular invasion
  - Bowel obstruction
  - <12 lymph nodes examined
  - T4 lesion
  - Tumor perforation
  - Inadequate or close surgical margins
“Personalized Medicine” (Molecular Diagnostics)

- Patient-Specific Tests
  - UGT-1A1 polymorphism

Dihydropyrimidine-dehydrogenase (DPD) deficiency

Schulz, C et al, Anti-Cancer Drugs 2009, 20:867-879

http://openi.nlm.nih.gov/detailedresult.php?img=3405332_13167_2010_41_Fig2_HTML&req=4
“Personalized Medicine” (Molecular Diagnostics) - continued

- **Tumor-Specific Tests**
  - Microsatellite Instability (MSI)
  - KRAS mutation analysis
    - Codons 12, 13, 61
  - Extended RAS testing
    - KRAS, NRAS
  - BRAF V600E mutation
  - Gene Signature Profiling
  - \( PIK3CA \) mutation

**Others:**
- Tumor Genomic Sequencing
- Circulating Tumor Cells (FDA-approved for mCRC in 2007)
Stage 0 or Stage I Colon Cancer

- Surgery
- Colonoscopy Surveillance
Stage II Colon Cancer
MSI Status is Prognostic

MSI and Adjuvant 5FU-based Chemotherapy

Stage II Colon Cancer


Surgical Resection, Stage II Colon Cancer

MSI-H
No chemotherapy after discussion with patient

MSI-Low/MSS

High-Risk Clinical & Pathological Features
Consider chemotherapy after discussion with patient

Molecular Risk Profile*

Moderate (>=5%) or small (3-4%) absolute benefit from chemotherapy
Consider chemotherapy after d/w patient

Very small (<3%) absolute benefit from chemotherapy
No chemotherapy after d/w patient

Stage II Colon Cancer: Chemotherapy considerations

- Multi-gene assay
  - QUASAR study*
  - 12-gene signature assay is prognostic for recurrence among stage II colon cancer patients
  - Genes include: FAP, INHBA, BGN, Ki-67, C-MYC, MYBL2, GDD45B + 5 reference genes.
  - Outcome: Low, Intermediate, High Risk

Stage III Colon Cancer:

- **Adjuvant chemotherapy:**
  - 5FU, leucovorin, oxaliplatin (FOLFOX)
    - Mosaic Trial\(^1\)
    - NSABP C-07\(^2\)
  - Capecitabine, oxaliplatin\(^3\) (CAPOX)
  - 6 months duration
  - **NO BIOLOGIC AGENTS**

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Therapeutic Prevention of CRC: Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

- Aspirin improves survival in \textit{PIK3CA}-mutant CRC patients


- Conflicting data have emerged
Historical Progress: Management of Advanced Colorectal Cancer

Supportive Care
- Median Survival: ~4-6 mo

1 Active Drug (5-FU/ LV, Capecitabine)
- Median Survival: ~10-12 mo

2 Active Drugs (5-FU/ LV + Oxaliplatin/ Irinotecan; Capecitabine + Oxaliplatin/ Irinotecan)
- Median Survival: ~15 mo

2 Active Drugs + bevacizumab
- Median Survival: ~20 mo

2/3 Active Drugs + Targeted/ Biologic Agents
- Median Survival: 20.3 mo

~24-31 mo

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
</tr>
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<tbody>
<tr>
<td><strong>Median Survival</strong></td>
<td>~4-6 mo</td>
<td>~10-12 mo</td>
<td>~15 mo</td>
<td>~20 mo</td>
<td>20.3 mo</td>
<td>~24-31 mo</td>
</tr>
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</table>
Vascular Endothelial Growth Factor (VEGF)

- **Bevacizumab**
  - Humanized monoclonal antibody targeting VEGF
  - Overall Response: none
  - Complications:
    - Bleeding, Thrombosis, Hypertension, Proteinuria
    - Wound dehiscence
    - Bowel perforation

- **Ziv-aflibercept** (VEGF-trap)
  - Recombinant fusion protein
  - Complications: as above

- **Regorafenib** (multikinase inhibitor) VEGFR/Raf/Kit/PDGFR

Agents bind or trap VEGF, reducing tumor angiogenesis.
VEGF-axis dependent and non-VEGF mediated mechanisms of resistance to anti-angiogenic therapies.
EGFR Monoclonal Antibodies

- **Cetuximab**
  - Overall Response = 10%
  - Complications:
    - Diarrhea
    - Skin toxicity
    - Infusion reactions
    - Hypomagnesemia
    - Interstitial lung disease

- **Panitumumab**
  - Overall Response = 10%
  - Complications:
    - Diarrhea
    - Skin toxicity
    - Hypomagnesemia

KRAS-wild type patients only!
Epidermal Growth Factor Receptor

# Prevalence of Mutations

<table>
<thead>
<tr>
<th></th>
<th>EXON 1</th>
<th>EXON 2**</th>
<th>EXON 3</th>
<th>EXON 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRAS</strong></td>
<td>12 13</td>
<td>44.9% (486/1083)</td>
<td>59 61</td>
<td>7.7% (41/534)</td>
</tr>
<tr>
<td><strong>NRAS</strong></td>
<td>12 13</td>
<td>2.2% (12/536)</td>
<td>59 61</td>
<td>0% (0/532)</td>
</tr>
</tbody>
</table>

- **18% (107/597) of KRAS exon 2 WT tumors have RAS Mutations**

* Prevalence is defined as mutations detected in a population of patients with WT KRAS exon 2 tumors whose tissues were deemed evaluable for RAS testing.
** The KRAS exon 2 data is from the overall population.
Stage IV Colorectal Cancer

- First-line:
  
  Chemotherapy + biologic
  
  - FOLFOX + bevacizumab,
  - FOLFIRI + bevacizumab
  - FOLFIRI + cetuximab or panitumumab if tumor is KRAS wild type

*In KRAS-wt, which regimen first – bevacizumab or cetuximab?

  - Cetuximab if KRAS-wt (FIRE-3)
    - Lancet 2014
  - Doesn’t matter: CALGB 80405
    - J Clin Oncol 32:5s, 2014 (suppl; abstr LBA3)
FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial

The Lancet Oncology, Volume 15, Issue 10, 2014, 1065 - 1075
http://dx.doi.org/10.1016/S1470-2045(14)70330-4
CALGB 80405: Chemo + Bev or Cetuximab in RAS-wt stage IV CRC

Overall Survival By Arm
(All RAS Wild Type Patients)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo + Bev</td>
<td>256 (178)</td>
<td>31.2 (26.9-34.3)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.40</td>
</tr>
<tr>
<td>Chemo + Cetux</td>
<td>270 (177)</td>
<td>32.0 (27.6-38.5)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Lenz, H, Proceedings at ESMO, Sept. 29, 2014, Madrid, Spain
Stage IV Colorectal Cancer

- **Second-line:**
  - Bevacizumab beyond progression (ASCO 2012)
    - FOLFOX-bev → FOLFIRI-bev
  - FOLFIRI-ziv-afibbercept
  - FOLFIRI + cetuximab or panitumumab (KRAS-wt)
  - Regorafenib
  - Clinical Trial *

- **Third-line and beyond**
  - Single agent cetuximab, or panitumumab
  - Regorafenib
  - Clinical Trial *
BRAF mutations define a unique CRC subtype

- BRAF mutations occur in a unique sub from serrated adenomas
  - Low rates of chromosomal instability,
  - High rates of hypermethylation
  - Common sporadic microsatellite instability

- The clinical challenges include low frequency (7% of mCRC) and aggressive biology
Atypical Location of Metastases and Poor Survival

Increased incidence compared to BRAF wild type

Liver | Lung | Peritoneum | Distant LNs | Brain

Hazard Ratio of 10.6 for OS
Less than 1 year OS

Tran, Kopetz, et al, Cancer ‘11
SWOG 1406: BRAF + EGFR

**Eligibility:**
1) BRAF V600 mutation
2) Prior treatment for metastatic disease
3) No more than 2 prior progression on chemotherapy
4) No prior cetuximab

**Stratified:**
1) Prior treatment with irinotecan

**Arm A:**
Cetuximab + Irinotecan

**Arm B:**
Vemurafenib + Cetuximab + Irinotecan

Optional cross-over

Historical response rate is <10% for cetuximab and irinotecan, with PFS of 2.4 months for BRAF\textsuperscript{mut}

Target HR 0.5 for PFS, with 2-sided alpha 5%, power 80%

N= 78 patients
Case Presentation #1 (Audience Response)

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Case Presentation #2

- 51 year female with Stage IVB (TxNxM1b) sigmoid adenocarcinoma (M1b due to multiple liver and lung metastases).

  - Tumor molecular profile:
    - MMR-proficient (MSS), RAS status (KRAS, NRAS) is wild type. BRAF-wt. ECOG performance status = 1.

- FOLFOX-bevacizumab chosen.
  - Admitted to hospital due to coronary vasospasm (5FU-intolerant).
Case Presentation #2 (continued)

- FOLFIRI-cetuximab chosen.
  - Small Bowel enteritis, pancytopenia

- Pharmacogenetic profile:
  - UGT 1A1 7,7 homozygous

- Current Regimen:
  - irinotecan (50% dose reduction) + cetuximab
Summary

- Personalized medicine for CRC is here (patient & tumor-specific factors)
- Stage I: surgery
- Stage II: surgery, then markers define treatment course (MSI status is key)
- Stage III: surgery + adjuvant chemotherapy; no role for biologic therapy.
- Stage IV: markers define treatment course (KRAS, BRAF); biologic agents are standard; multimodal treatment often indicated.