EGFR, K-RAS, BRAF Testing In The Elderly: Same As in Younger Patients?

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Outline

- Colorectal cancer (CRC) burden in older individuals
- Chemotherapy options
- Biologic therapy options
- Molecular targets
- Testing in older vs. younger individuals with CRC
- Conclusions
Disclosures

- None
CRC burden in older individuals

- Annual incidence 150k USA, 1 million worldwide
- Majority of patients are elderly
  - Median age at diagnosis 72 years
  - 12% older than 85 years
Emerging phenotype of CRC: Genetic

- Genetic instability
  - Microsatellite instability (MSI-H)
    - Loss of DNA mismatch repair (e.g. hMLH1, hMSH2, hMSH6)
  - Chromosomal instability (CIN)
    - Loss of heterozygosity (LOH), hypomethylation in tumor cell

Popat JCO 2006; Sargent JCO 2008; Ribic NEJM 2003; Samowitz Gastro 2005
Emerging phenotype of CRC: Epigenetic

- Epigenetic instability

CpG Island Methylator Phenotype (CIMP)
- Hypermethylation of promoter regions
- Leads to silencing of tumor suppressor genes
- Associated with BRAF and KRAS mutations
- Independent of and inversely related to CIN
- Variably related to MSI-H

Popat JCO 2006; Sargent JCO 2008; Ribic NEJM 2003; Samowitz Gastro 2005
Tumor biology differs by age

- Increased CIMP with age

- Associated with poor prognostic factors
  - BRAF mutation
  - Proximal tumor site
  - Poor histology
  - Advanced stage

- 2-fold higher for age 70+
  - controlling for stage, histology, tumor site, KRAS/BRAF/p53 mutation

Samowitz Gastro 2008; Nagasaka JCO 2005; Popat JCO 2006; Goel Gastro 2007
Differing response to treatment

- Differing tumor biology potentially explains differing response to CRC treatment among older and younger individuals

- Metastatic vs. adjuvant setting
  - Chemotherapy
  - Biologics
    - Focus on EGFR antibodies
Metastatic CRC, Chemotherapy - Benefit

- Metastatic setting
  - Folprecht JCO 2008 - N=2,692 (22% ≥ 70 yrs)
    - 4 trials of irinotecan-based therapy
    - Improved PFS, trend to improved OS for elderly w/addition of irinotecan
  - Goldberg JCO 2006 - N=3,742 (16% ≥ 70 yrs)
    - 4 trials of oxaliplatin-based therapy
    - Similar survival benefit and toxicity in age subgroups
Adjuvant CRC, 5-FU - Benefit

- **Adjuvant setting**
  - Sargent NEJM 2001 – N=3351 (15% ≥ 70 yrs)
    - 7 trials of 5-FU + levamisole/leucovorin v surgery
    - No significant interaction observed between age and efficacy of treatment
Adjuvant CRC, Combination Chemotherapy – Lack of added benefit

- ACCENT

- Updated with 6 combination/oral fluoropyrimidine trials

- 12,669 pts accrued from 1997-2002

- 17% ≥70 years

## Efficacy – oxaliplatin-based therapy

<table>
<thead>
<tr>
<th>Age</th>
<th>Experimental vs Control IV 5-FU/LV</th>
<th>Endpoint HR (95% CI)</th>
<th>Deaths within 6 mo Exp vs Control % (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td>DFS*</td>
<td>0.77 (0.68, 0.86)</td>
<td>0.81 v 0.81 (p=1.0)</td>
</tr>
<tr>
<td>n = 3,977</td>
<td>OS*</td>
<td>0.81 (0.71, 0.93)</td>
<td></td>
</tr>
<tr>
<td>≥ 70</td>
<td>TTR*</td>
<td>0.76 (0.67, 0.86)</td>
<td></td>
</tr>
<tr>
<td>n = 703</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction</td>
<td>DFS*</td>
<td>1.04 (0.80, 1.35)</td>
<td>2.57 v 1.37 (p=0.25)</td>
</tr>
<tr>
<td>of age by</td>
<td>OS*</td>
<td>1.19 (0.90, 1.57)</td>
<td></td>
</tr>
<tr>
<td>treatment</td>
<td>TTR*</td>
<td>0.92 (0.69, 1.23)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>0.016</td>
<td>0.037</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.037</td>
<td>0.21</td>
</tr>
</tbody>
</table>

* Values < 1 favor experimental arm
STEPP analysis – Oxaliplatin therapy

P = value = 0.33
CRC treatment in older individuals
- Biologics

Cetuximab (Erbitux)

Panitumumab (Vectibix)

Expression of EGFR not predictive

- Effective in 10-20% of chemo-refractory cases
- KRAS mutation accounts for 30-40% of non-responsive cases
- BRAF mutations may account for additional 12%
- Etiology for remaining failures is not yet known
KRAS/ BRAF mutation is predictive

- KRAS
  - Test for activating mutation of KRAS codon 12 or 13

- BRAF
  - Test for BRAFV600E mutation
## KRAS mutation - predictive

<table>
<thead>
<tr>
<th>Drug</th>
<th>KRAS WT</th>
<th>KRAS Mut</th>
<th>HR (WT vs. M)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cetuximab</strong></td>
<td>N</td>
<td>117</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>RR, %</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>mPFS, mo</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td><strong>Panitumumab</strong></td>
<td>N</td>
<td>124</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>RR, %</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>mPFS, wks</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td><strong>Xelox/A ± C</strong> (CAIRO2)</td>
<td>N</td>
<td>153</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>RR, %</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>mPFS, mo</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td><strong>FOLFIRI ± C</strong> (CRYSTAL)</td>
<td>N</td>
<td>172</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>RR, %</td>
<td>59</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>mPFS, mo</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td><strong>FOLFOX ± C</strong> (OPUS)</td>
<td>N</td>
<td>61</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>RR, %</td>
<td>61</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>mPFS, mo</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>

Reformatted from Allegra JCO 2009; Lievre JCO 2008; Bokemeyer JCO 2009; van Cutsem JCO 2007
KRAS mutation - not clearly prognostic

- Inconsistent data supporting activating mutation in KRAS affecting outcome, independent of therapy
  - Similar survival for KRAS WT vs. Mut
    - mPFS 7.3 wks for both groups in best supportive care arm of panitumumab study
    - mPFS 1.8 mo for both groups in best supportive care arm of cetuximab study

KRAS Mutation Testing

- Acceptable samples
  - Freshly extracted
  - Rapidly frozen
  - Formalin fixed, paraffin embedded

- Acceptable assays
  - Real-time polymerase chain reaction
  - Direct sequencing analysis

Jimeno JCO 2009
Testing Recommended

- **ASCO Provisional clinical opinion (JCO 2009)**
  - All pts with mCRC should have testing for KRAS mutations in CLIA-accredited lab
  - Pts should not receive anti-EGFR Ab therapy if mutation in codon 12/13

- **Limitations**
  - Does not reflect data regarding activating KRAS mutations at codons 61, 146
  - Does not reflect contribution of other genetic alterations affecting response to anti-EGFR MoAbs
  - No FDA-approved assay; Institution lab choice

Allegra JCO 2009; http://www.cap.org/POET
www.bcbs.com/blue resources.tec.press.KRAS-mutations-epidermal.html
Need for standardization – sample selection

- Process of fixation affects DNA stability
- Mutation rate in formalin-fixed paraffin-embedded tissue less than in frozen tissue

Allegra JCO 2009; Jimeno JCO 2009; gallegos Cell Oncol 2007
Need for standardization - assay selection

- Sensitivity, Specificity of KRAS mutation testing assays vary
- PCR requires higher mutant-to-wild type copies for amplification
- Alternate options
Need for standardization - patient selection

- No age correlation
- Age 70+ excluded from CRYSTAL (FOLFIRI ± C in mCRC) given DSMB concerns at interim analysis

NCIC CO.17:
- N=572, 41% 65+, 25% with comorbid condition
- Similar overall survival benefit by age for C vs. BSC
- Neither age nor comorbidity prognostic

Jimeno JCO 2009; Goldberg ASCO 2009; Powell ASCO 2009
Is age a factor in mutation testing?

- Genetic/epigenetic alterations predict response to anti-EGFR MoAb therapy
- Age is poor prognostic factor in CRC
- Unclear if age is prognostic in context of EGFR/KRAS/BRAF mutations OR predictive in context of anti-EGFR MoAb
- Standardization of testing imperative, particularly in this prevalent population
Acknowledgements

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Questions/Comments