Third Line and Beyond: Management of Refractory Colorectal Cancer

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Stanford University
Overview

- Defining the chemo “refractory” and “intolerant”
- Agents approved in 3rd line setting
- Off label usage and agents in development
- Immunotherapy
65 yo with "refractory" metastatic colon cancer

- Stage III sigmoid colon cancer resected and s/p 6 months of FOLFOX
- Ten months later: "unresectable liver and lung mets"
- Biopsy confirmed colon and KRAS mutation (G13D), Mismatch Repair (MMR) Protein proficient (i.e. MSS)
- FOLFIRI + bevacizumab x 10 months with initial response then progression
Which strategy is most likely to achieve a minor response or better...

A) Send tumor for molecular profiling (e.g. DNA sequencing) and treat any "actionable" finding

B) Try EGFR antibody since G13D RAS mutation not truly a resistance marker

C) Try oxaliplatin as single agent since tumor refractory to 5FU

D) Try regorafenib since refractory to cytotoxic chemo

E) Try FOLFOX or CAPOX since no proof of resistance
Considerations in evaluating the “refractory” patient...

- Is tumor actually refractory?
  Oxaliplatin given as adjuvant: has it be retried?
  Oxaliplatin d/c’d for neuropathy (as in OPTIMOX): has neuropathy resolved?
  Oxaliplatin d/c’d for hypersensitivity reaction: worth trying “desensitization” protocols?

- Have drugs been used at “optimal” doses?
  5-FU / capecitabine: if no toxicity, push the dose or try capecitabine + bevacizumab if 5-FU refractory

- Is tumor potentially resectable or amenable to liver directed therapies (radioembo, chemoembo, thermal ablation)?
A few other clinically challenging scenarios

- 38 yo with RAS mutated MMR proficient (i.e. MSS) metastatic colon has chest pain with exertion while on capecitabine; Stress Echo shows ST changes while on capecitabine; cardiac cath is normal

- Prior treatments include:
  FOLFIRI + bevacizumab as first line therapy (with some anginal symptoms noted but not reported at that time)
  CAPOX x 1 (during which he had cardiac workup above)

- He has bulky liver metastases and slowly increasing abdominal discomfort and LFT’s: bilirubin 1.5
You’re best option now is:

A) continue oxaliplatin as a single agent

B) try regorafenib

C) give TAS102 with oxaliplatin

D) start a Calcium Channel Blocker and resume CAPOX
Another example of “intolerance” to 5-FU

- 47 yo with RAS wildtype MMR proficient rectal cancer has small volume asymptomatic lung mets and gets FOLFOX and bevacizumab as first line therapy. On day 7, he is admitted with hypotension, dehydration, diarrhea, stomatitis, fever and neutropenia.

- After a week long ICU stay he recovers and you presume that he has a homozygous DPD (dihydropyrimidine dehydrogenase) deficiency. CEA declined from 135 to 62.

- He then gets irinotecan and cetuximab x 2 months but has radiographic and marker progression
You now choose:

- A) Regorafenib
- B) Bevacizumab as single agent
- C) Capecitabine at 500 mg po bid on days 1 and 2 q 2 weeks; increase as tolerated...
- D) TAS102 at standard dose
Agents approved in 3\textsuperscript{rd} line setting

- Regorafenib

- TAS 102 (trifluridine/tipiracil)

- Cetuximab + irinotecan; panitumumab single agent

FDA approved agents that can be considered in 3\textsuperscript{rd} line
Capecitabine +/- bevacizumab
Regorafenib: The CORRECT Trial

Metastatic CRC
Measurable disease
Refractory or intolerant to irinotecan, oxaliplatin and if RAS wt EGFRi

505 pts → Regorafenib 160 mg po + BSC

2:1

255 pts → Placebo + BSC

Primary Endpoint: Overall Survival

Grothey et al. Lancet 2013
Overall survival: Regorafenib vs Placebo

Median OS: 6.4 vs 5.0 months
HR: 0.77 (CI 0.64-0.94); p=0.0052

Grothey et al. Lancet 2013
Progression Free Survival: CORRECT Trial

HR 0.49 (CI 0.42-0.58)
P<0.0001

Grothey et al. Lancet 2013
Trifluridine/Tipiracil (TAS102)

Metastatic CRC
Measurable disease
After ≥ 2 prior regimens
including oxali, iri, bev, and if RAS WT, EGFR antibody
ECOG 0,1

534 pts

TAS102: 35 mg/m² po + BSC

265 pts

Placebo + BSC

2:1

R

Primary Endpoint: Overall Survival

Mayer et al. NEJM 2015
TAS-102 vs placebo: overall survival

Median OS: 7.1 vs 5.3 months
HR: 0.68 (0.58-0.81); p<0.001

Mayer et al. NEJM 2015
Progression Free Survival: TAS102

Hazard ratio for progression or death, 0.48 (95% CI, 0.41–0.57)
P<0.001 by log-rank test

Mayer et al. NEJM 2015
### Grade 3 or higher adverse events: Beware of cross trial comparison

<table>
<thead>
<tr>
<th></th>
<th>Regorafenib</th>
<th>TAS102</th>
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</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>14%</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>NR</td>
<td>3%</td>
</tr>
<tr>
<td>Hand foot skin</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>Rash / desquamation</td>
<td>6%</td>
<td>NR</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7%</td>
<td>NR</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>NR</td>
<td>38%</td>
</tr>
<tr>
<td>Anemia</td>
<td>2%</td>
<td>18%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3%</td>
<td>8%</td>
</tr>
<tr>
<td>Any event / any grade</td>
<td>51% (placebo 61%)</td>
<td>69% (placebo 52%)</td>
</tr>
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</table>
Progression Free Survival: “3rd line” agents

Regorafenib

TAS102

Cetuximab

Panitumumab

- Hazard ratio: 0.69 (95% CI: 0.49-0.94)
- p-value: <0.0001

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Med PFS (mos)</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Cetux + BSC</td>
<td>1.9</td>
<td>1.8–2.1</td>
</tr>
<tr>
<td>BSC alone</td>
<td>1.8</td>
<td>1.6–1.9</td>
</tr>
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Stratified log rank p-value < 0.0001
Off Label Options / Experimental Options

- BRAF mutated tumors
- Her-2-neu amplified or activated mutations
- MATCH trial options
- MSI or hypermutated tumors
New Targets in Trials: BRAF

~8% of metastatic colon cancers
Often more aggressive biology

BRAF inhibitors approved in melanoma
BRAFi + MEKi + EGFRi more efficacious

Still need to identify the optimal combination of agents
New Targets in Trials: Her 2-neu

- Her 2-neu overexpressed in ~ 25% of breast cancers but only ~ 5% of metastatic colon cancers
  - perhaps higher percentage in left sided colon cancers...

- Trastuzumab (antibody to her-2) and lapatinib (kinase inhibitor of her-2) used in Her 2-neu (+) colon cancers
  8 of 27 patients responded (35%)
  Disease control rate (stable disease + responders) = 78%

Siena et al; ASCO 2015
Science

BREAKTHROUGH OF THE YEAR

Cancer Immunotherapy

This year marks a turning point in cancer, as long-sought efforts to unleash the immune system against tumors are paying off—even if the future remains a question mark.

Cover of Science, 19 December 2013

Stanford Cancer Institute
New Targets in CRC: “Checkpoint” proteins

Turning up The Activating

Blocking the Inhibiting
Mutational Burden in Tumors

Adapted from Lawrence et al. Nature 2013
Mutational Burden in Tumors

Lawrence et al. Nature 2013
Hypothesis

- Mutations encode proteins that can be recognized and targeted by the immune system

- Most tumors have dozens of mutations while mismatch repair deficient tumors harbor thousands of mutations

- Immune augmentation by PD-1 blockade may be highly effective in mismatch repair deficient tumors
Mismatch Repair Deficiency

- Microsatellite instability in tumor cells is due to deficient DNA mismatch repair
  - **Germline** mutations (Lynch syndrome) and/or
  - **Sporadic** mutations (MLH1, MSH2, MSH6, PMS2)
  - **Epigenetic** silencing (MLH1 hyper-methylation)
Mismatch Repair Deficiency

- Microsatellite instability in tumor cells is due to deficient DNA mismatch repair
  - **Germline** mutations (Lynch syndrome) and/or
  - **Sporadic** mutations (MLH1, MSH2, MSH6, PMS2)
  - **Epigenetic** silencing (MLH1 hyper-methylation)
Anti-PD-1 in repair deficient cancers

Study Design

<table>
<thead>
<tr>
<th>Colorectal Cancers</th>
<th>Non-Colorectal Cancers</th>
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<tbody>
<tr>
<td><strong>Cohort A</strong></td>
<td><strong>Cohort B</strong></td>
</tr>
<tr>
<td>Deficient in</td>
<td>Proficient in</td>
</tr>
<tr>
<td>Mismatch Repair</td>
<td>Mismatch Repair</td>
</tr>
<tr>
<td>N=25</td>
<td>N=25</td>
</tr>
</tbody>
</table>

| **Cohort C**       |
| Deficient in       |
| Mismatch Repair    |
| N=30               |

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Primary endpoint: immune-related 20-week PFS rate and response rate
- Mismatch repair testing using standard PCR-based test for detection of microsatellite instability

Non-colorectal types: endometrial (9), gastric (3), small bowel (4), ampullary/biliary (7), pancreas (4) sarcoma (1), prostate (1), gliomas (1)
### Objective Responses

<table>
<thead>
<tr>
<th></th>
<th>MMR-deficient CRC</th>
<th>MMR-proficient CRC</th>
<th>MMR-deficient non-CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N )</td>
<td>25</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>Objective Response Rate</td>
<td>62%</td>
<td>0%</td>
<td>53%</td>
</tr>
<tr>
<td>Disease Control Rate</td>
<td>92%</td>
<td>16%</td>
<td>70%</td>
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Diaz, L. et al. NEJM June 2015

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Presented By Dung Le at 2015 ASCO Annual Meeting
47 yo nurse with Lynch and met CRC

Refractory to FOLFOX + bev; FOLFIRI + cetuximab

Progressive weight loss, pain, fatigue, decline in performance status.

On MS contin 60 tid with MS elixer for breakthrough back and abdominal pain

Scan with carcinomatosis, retroperitoneal adenopathy and left adrenal mass
Before and after 4 months of anti-PD1
60 yo with poorly differentiated NET arising from colon

Stage I and stage II colon cancers s/p resection
CT 4 weeks later with new liver lesions
Biopsy: poorly differentiated NET
Review of stage I lesion confirmed same with Ki-67 > 50%
Cisplatin + etoposide x 2 months with progression of disease
Both NET and adenoca found to be MSI
Entered on to PD1 trial using pembro

CT prior to and MRI after 4 months of pembro
8 visible lesions largest 4 cm now
down to 2 lesions, largest 4 mm
Conclusions

- Not all chemo "refractory" tumors are refractory
- Not all chemo “intolerant” patients are intolerant
- Modest benefits with new third line agents

- Strategies to treat BRAF mutated tumors evolving
- Her 2 neu may be target worth searching for…
- Hypermutated tumors (via MSI or other) can be highly responsive to checkpoint blockade
- Consult multidisciplinary teams for resection / ablation and embolization options
Cell-Cell Communication via cell surface “checkpoint” proteins
Thank you...