Targeted and Chemotherapeutic Approaches to Management of Metastatic Colorectal Cancer

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Fox Chase Cancer Center
Learning Objectives

• **Critically evaluate** current clinical trial evidence supporting the use of targeted and chemotherapeutic approaches, and their combinations, in the management of metastatic colorectal cancer (mCRC) across multiple lines of treatment.

• **Explain** which factors driving patients’ segmentation (prognostic and predictive biomarkers, comorbidities, patients’ preference) impact the treatment decision-making process in different clinical scenarios across disease progression.

• **Review** current best practices for the management of adverse effects associated with targeted therapies in mCRC and how to maximize tolerability and adherence to different therapeutic regimens.
Case: F.F.

• 49 year old otherwise healthy man presented with constipation for 3 months and abdominal pain.
• 30 lb weight loss over the last 3 months.
• Low grade fever, increasing right upper quadrant pain
Case: F.F.

- CEA- 702
- LFT mildly elevated, bilirubin normal

- Colonoscopy nearly obstructive mass in the recto-sigmoid junction
- Biopsy – moderately differentiated adenocarcinoma
Worldwide Cancer Statistics

Epidemiology

- Estimated US incidence (new cases): 142,820
- Estimated US mortality: 50,830
- Third most common malignancy in man and woman.

Epidemiology

5-yr survival for metastatic disease is about 10%

Colon Cancer: More Than One Disease

- Molecular
  - MSI vs MSS
  - RAS WT vs MUT

- Anatomic
  - Right versus left
  - Rectal versus colon
Right vs. Left: Sidedness Matters

Median age at diagnosis:
- Right sided: 70.2 years
- Left sided: 65 years

Pre-Treatment Evaluation in mCRC

Imaging:
- CT chest/abdomen/pelvis
- PET-CT and MRI useful for specific questions i.e. resection.

Lab/Pathology/Molecular testing
- Confirm path/ biopsy of metastases
- Baseline CEA
- KRAS mutation status (all patients) prior to anti-EGFR therapy
- BRAF mutation (?)
- MSI status
- UGT1A1*28 (not recommended routinely, consider before irinotecan)
Resection of Primary Tumor in mCRC

- C-10 phase II multicenter study.
- 86 patients, front line FOLFOX+Bev with intact primary tumor.
- Primary end point surgical resection required due to symptoms related to primary tumor.

<table>
<thead>
<tr>
<th>Event</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery due to symptoms from primary tumor</td>
<td>10</td>
<td>11.6</td>
</tr>
<tr>
<td>Death with symptoms from primary tumor</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>Primary tumor resected with curative intent</td>
<td>8</td>
<td>9.3</td>
</tr>
<tr>
<td>Patient died with intact tumor</td>
<td>28</td>
<td>32.6</td>
</tr>
<tr>
<td>Patient was alive at last follow up with intact tumor</td>
<td>35</td>
<td>40.7</td>
</tr>
</tbody>
</table>

Resection of Metastatic Site

- Data from MD Anderson + Mayo 2,470 patients. 231 underwent hepatic resection.
- Rates of resection increased.
- Survival improved with resection.

Treatment – Conversion to Surgery

Original article

Chemotherapy permits resection of metastatic colorectal cancer: experience from Intergroup N9741

T. Delaunoit¹, S. R. Alberts¹, D. J. Sargent²*, E. Green², R. M. Goldberg³, J. Krook⁴, C. Fuchs⁵, R. K. Ramanathan⁶, S. K. Williamson⁷, R. F. Morton⁸ & B. P. Findlay⁹

Original article

Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients

C. Pozzo¹, M. Basso¹, A. Cassano¹, M. Quirino¹, G. Schinzari¹, N. Trigila¹, M. Vellone², F. Giuliani², G. Nuzzo² & C. Barone¹*
Advances in the Treatment of mCRC

Over the years, there have been significant improvements in the treatment of metastatic colorectal cancer (mCRC). In the early years (1980-1995), the primary treatment was Best supportive care (BSC) and 5-FU. Over time, newer agents such as Irinotecan, Capecitabine, Oxaliplatin, Cetuximab, Bevacizumab, Panitumumab, Ziv-Aflibriccept, Regorafenib, Ramucirumab, and TAS-102 have been introduced, each contributing to an increase in median overall survival.

The diagram illustrates the timeline of treatment advancements and the corresponding increase in median overall survival from the early years to the present day (2015).
More Agents Available Now...

- BSC
- Fluoropyrimidine
- Irinotecan
- Oxaliplatin
- Bevacizumab
- Cetuximab
- Regorafenib / TAS-102
- Aflibercept / Ramucirumab
- Panitumumab
More Agents Available Now...

Ongoing debate between the “best” schedule and sequencing of these agents
Self Reflection

• Let’s take a moment to think about patients you have treated.
Self Reflection

• Let’s take a moment to think about which medicines they have been on.
2005 Update: 11 Phase 3 Trials – 5768 pts

OS (months) = 13.2 + (% patients with 3 drugs × 0.1), R² = 0.85

First-Line Therapy
- Infusional 5-FU/LV + Irinotecan
- Infusional 5-FU/LV + Oxaliplatin
- Bolus 5-FU/LV + Irinotecan
- Irinotecan + Oxaliplatin
- LV5FU2
- FOLFOXIRI
- CAIRO

Addition of Irinotecan

PFS: 4.3m vs. 7.0m (p=0.004)
OS: 12.6m vs. 14.3m (p=0.04)

Addition of Oxaliplatin

Progression free survival
9.0 vs 6.2m p=0.0003

Overall survival
16.2 vs 14.7m p=NS

F.F. Treatment Plan

• Metastatic adenocarcinoma, multiple liver metastasis (10+)
• MSS
• KRAS wild type
• Discussion with oncologist.
  – Goal: best shot to live as long as possible; needs to keep working; insurance carrier for family
  – Has teenage children in high school
  – Decision to avoid surgery and initiate FOLFIRI/Cetuximab
Self Reflection

• Think about your practice.
Biologic Agents- Monoclonal Antibodies

Murine Ab “momab”
Chimeric mouse-human Ab “ximab”
Humanized Ab “zumab”
Human Ab “mumab”

Fc
Fab

Anti-EGFR
Anti-VEGF

Cetuximab
Panitumumab
Bevacizumab

EGFR Targeted Therapy

EGFR Targeted Therapy

FOLFIRI Cetuximab

- Port placement
- Given every 14 days
- Infusion room time and 46 hour infusion at home
- Pre-meds
- Anti-emetics for home
Diarrhea

- Brat diet
- Imodium
- Lomotril
- Hydration
- Check electrolytes
- Review other medications (antihypertensives, diuretics)
- Consider admission when needed

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Increase of &lt;4 stools per day over baseline</td>
</tr>
<tr>
<td>Grade II</td>
<td>Increase of 4-6 stools per day over baseline</td>
</tr>
<tr>
<td>Grade III</td>
<td>Increase of &gt;7 stools per day over baseline; hospitalization indicated; limits self care ADL’s</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Life-threatening consequences; urgent intervention</td>
</tr>
<tr>
<td>Grade V</td>
<td>Death</td>
</tr>
</tbody>
</table>
Adverse Effects of EGFR Inhibition

• Cutaneous adverse effects
  – Papulopustular reaction involving skin
  – Can affect compliance and QOL
  – Leaves skin vulnerable to bacterial overgrowth and infection
  – Skin rash can lead to dose modification or treatment discontinuation
  – Sun protection
  – Topical clindamycin 2% / 1% hydrocortisone cream
  – Oral doxycycline if moderate to severe
  – Consider dermatology if needed

• Dry eyes
Case: F.F.

- First CT at 3 months with great response to treatment
- Stable disease after 9 months
- Increasing diarrhea and neutropenia requiring Neulasta
- Restaging CT 2 months later for new cough. New pleural effusion + malignancy
But What Impacts the Patient’s Decision Making?

• Patient goals
• Quality of life
• Side effect profile of drugs
• Comorbid conditions
• Logistics
Self-Reflection

• Think about this in regards to your patients
Next Steps in Treatment

- FOLFOX/bevacizumab
- PleurX catheter placement
- Palliative care consult
- Patient education
VEGF Inhibitors

- PIGF
- VEGF-B
- VEGF-A
- VEGF-R1 (FLT1)
  - Migration
  - Invasion
  - Survival
- VEGF-R2 (KDR/Flk-1)
  - Proliferation
  - Survival
  - Permeability
- VEGF-R3 (FLT4)
  - Lymphangiogenesis

VEGF Inhibitors:
- Bevacizumab
- Ramucirumab
- Afiblercept (VEGF Trap)
- Regorafeib

Bevacizumab Risks

- Hypertension (~20%)
- Arterial thrombosis (2-5%)
  - SCD, MI, CVA, TIA
  - Increased with poor PS or age > 65
- GI perforation (1-2%)
- Grade 3-4 bleeding (2-5%)
- Post-operative bleeding/wound healing (1-2%)
  - Perforation, fistula, abscess, surgery within 60 days

Nursing Implications for the Patient Receiving FOLFOX

• Patient education
  – Nausea
  – Diarrhea
  – Cold sensitivity

• Ask about peripheral neuropathy
  – Assessment CTCAE grading
  – Management

• Infusion pump safety
Peripheral Neuropathy

- Numbness
- Tingling
- Pain
- Like walking on broken glass
- Off balance
- Stiffness
## CTCAE v4.0 Peripheral Neuropathy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Asymptomatic, lost of DTRs or paresthesia</td>
</tr>
<tr>
<td>II</td>
<td>Moderate symptoms; limiting instrumental ADL’s</td>
</tr>
<tr>
<td>III</td>
<td>Severe symptoms limiting self care ADLs</td>
</tr>
<tr>
<td>IV</td>
<td>Life – threatening consequences</td>
</tr>
<tr>
<td>V</td>
<td>Death</td>
</tr>
</tbody>
</table>
Management Strategies

• Assessment via CTCAE
• Considering of modification of dose/holding drug
• Gabapentin, duloxetine, pregabalin
• PT/OT
• B-complex
Case: F.F.

- Disease progression after 9 months of FOLFOX/bevacizumab
- HTN managed with ACE inhibitor
- Grade II peripheral neuropathy - stable
- Middle child graduated from high school
- New lung metastasis and increasing liver metastasis
Self-Reflection

• Think about when you’ve been with a patient at a time of progression and they need to think about next treatments; what worries have they shared with you?
F.F. Treatment Decision

- Consideration of clinical trial
- TAS 102
- Regorafenib
RE COURSE: TAS-102 in Refractory mCRC

Stratification
- Region
- KRAS status
- Time from diagnosis of mets to randomization

Primary Endpoint: OS

TAS-102 Treatment Schedule
35mg/m² BID 5 days per week with 2 days rest, 2 weeks on 2 weeks off.

RE COURSE: TAS-102 in Refractory mCRC – PFS

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>38%</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>4%</td>
</tr>
<tr>
<td>Anemia</td>
<td>18%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hand foot syndrome</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac ischemia</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4%</td>
</tr>
</tbody>
</table>

RECOURSE: TAS-102 in Refractory mCRC – Overall Survival

Nursing Considerations with TAS-102

- Patient education for schedule
  - Calendars
  - Prefer a Monday start date (M-F, M-F, off 2 weeks)
- Watch for s/s of bleeding
- Diarrhea management
- Labs
  - Labs at Day 14 and prior to start of next cycle
Regorafenib Multikinase Inhibitor

Biochemical Activity | Regorafenib IC$_{50}$ mean ± SD nmol/L (n)
--- | ---
VEGFR1 | 13 ± 0.4 (2)
Murine VEGFR2 | 4.2 ± 1.6 (10)
Murine VEGFR3 | 46 ± 10 (4)
TIE2 | 311 ± 46 (4)
PDGFR-β | 22 ± 3 (2)
FGFR1 | 202 ± 18 (6)
KIT | 7 ± 2 (4)
RET | 1.5 ± 0.7 (2)
RAF-1 | 2.5 ± 0.6 (4)
B-RAF | 28 ± 10 (6)
B-RAF$^{V600E}$ | 19 ± 6 (6)

**CORRECT Study Design**

- Multicenter, randomized, double-blind, placebo-controlled, Phase 3
  - 2:1 randomization
  - Stratification factors: prior anti-VEGF therapy, time from diagnosis of metastatic CRC, geographical region
- Global trial: 16 countries, 114 active centers; 1052 screened, 760 enrolled
- Secondary endpoints: PFS, ORR, DCR

CORRECT: Overall Survival

Survival Distribution Function

Days From Randomization

Placebo N = 255
Regorafenib N = 505

Median Survival
Placebo: 5.0 months
Regorafenib: 6.4 months

95% CI
Placebo: 4.4 - 5.8
Regorafenib: 5.9 - 7.3

Hazard ratio: 0.77 (95% CI, 0.64-0.94)

P = 0.0052

CORRECT: PFS

Survival Distribution Function

Regorafenib | Placebo
---|---
Median PFS | 1.9 m | 1.7 m
Hazard ratio: 0.49 (95% CI, 0.42-0.58)
1-sided \( P<0.000001 \)

Placebo N = 255
Regorafenib N = 505

## CORRECT: Adverse Events

<table>
<thead>
<tr>
<th>Adverse event, %</th>
<th>Regorafenib N = 500</th>
<th>Placebo N = 253</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Hand–foot skin reaction</td>
<td>46.6</td>
<td>16.6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>47.4</td>
<td>9.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27.8</td>
<td>7.2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33.8</td>
<td>7.0</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>26.0</td>
<td>5.8</td>
</tr>
<tr>
<td>Anorexia</td>
<td>30.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Mucositis, oral</td>
<td>27.2</td>
<td>3.0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Fever</td>
<td>10.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>14.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Bleeding</td>
<td>11.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Voice changes</td>
<td>29.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Weight loss</td>
<td>13.8</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Management of Patients on Regorafenib

- Home BP log; weekly BP checks in office.
- Skin care
- Weekly LFT’s for first 2 cycles
- Safe administration (calendars)
- Hand-foot skin reaction
- Treatment of diarrhea
# Hand-Foot Syndrome

<table>
<thead>
<tr>
<th>AE Term</th>
<th>Definition</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade I</strong></td>
<td>Changes or dermatitis without pain</td>
<td>• Udder cream, Eucerin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Monitor</td>
</tr>
<tr>
<td><strong>Grade II</strong></td>
<td>Skin changes with pain limiting function</td>
<td>• Hold drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Resume when grade I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Moisturize</td>
</tr>
<tr>
<td><strong>Grade III</strong></td>
<td>Severe skin changes with pain limiting ADLs</td>
<td>• Hold drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Moisturize</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Treat pain, topical lidocaine</td>
</tr>
</tbody>
</table>
Self-Reflection

• Think about the patients you’ve had. Have they ever had hand-foot syndrome? How does this impact your practice?
Microsatellite Instability

- Hypermutable phenotype
  - 10-100X somatic mutation rate
- Characterized by loss of DNA mismatch repair activity and simple repetitive sequences of DNA
- More likely to be:
  - Right-sided/proximal colon
  - Poorly differentiated
  - Younger, female patients
  - Contain lymphocyte infiltrates
- Less likely to be KRAS or p53 mutated
- Associated with hereditary colon cancer syndromes (Lynch Syndrome)
- Overall better prognosis

Immunotherapy

• 10-15% of sporadic colon cancers will have microsatellite instability
• Pembrolizumab IV infusion given every 3 weeks
Summary

• The prognosis of patients with mCRC has improved over the last decade.
• Standard of care in the 1st and 2nd line setting: combination chemotherapy and biologic agent
• Additional studies are needed for identification of novel targets and better biomarkers
THANK YOU!