Diagnosis and Management of Metastatic Colorectal Cancer:

State-of-the-Art Oncology Nursing Practice

(Includes NCCN 1.2015 Guideline Update)
Faculty

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Philadelphia, Pennsylvania
Objectives

Upon completion of this educational activity, learners should be better able to:

1. Distinguish guideline-recommended treatment options for metastatic colorectal cancer (mCRC) and the evidence that supports each therapy

2. Summarize recent changes to current mCRC guidelines, including the addition of new therapeutic options and opportunities for more targeted therapy in select patient populations

3. Recognize toxicities associated with chemotherapy and targeted therapies for the treatment of mCRC and develop individual plans to manage these complications

4. Identify and distinguish resources and guidelines designed to manage treatment-related toxicities in mCRC therapy
Disclosures

- **Ms. Grande:**
  - Research (subinvestigator): Bayer Healthcare Pharmaceuticals; Exelixis, Inc.; Novartis Pharmaceuticals; Roche Pharmaceuticals; Eisai, Inc.

- **Planners and managers for this activity have no relevant relationships to disclose**
Commercial Support Statement

- This activity is supported by an educational grant from Bayer HealthCare Pharmaceuticals
Colorectal Cancer Incidence

- An estimated 96,830 colon cancer and 40,000 rectal cancer cases will be diagnosed in 2014\(^1\)
  - 50%-60% of people diagnosed with colorectal cancer (CRC) will develop metastatic disease\(^2\)
  - Metastatic disease most frequently occurs after treatment for locoregional disease\(^3\)
  - Most common site of metastasis is the liver\(^4,5\)
  - 20%-34% of people with CRC present with synchronous liver metastases\(^5,6\)

- CRC is third most common cancer diagnosed in men and women\(^1\)

CRC Development: Progression From Adenoma to Carcinoma

First somatic \textit{APC} mutation or loss  
Second \textit{APC} mutation or loss  
\textit{KRAS} mutation  
\textit{DCC} loss  
Further changes

Normal mucosa

Hyperproliferative epithelium

Adenoma, increasing in size and dysplasia

Carcinoma

## Tumor, Node, Metastasis (TNM) staging of CRC

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Stage I Diagram" /></td>
<td><img src="image2" alt="Stage II Diagram" /></td>
<td><img src="image3" alt="Stage III Diagram" /></td>
<td><img src="image4" alt="Stage IV Diagram" /></td>
</tr>
<tr>
<td><strong>T1</strong>: limited to mucosa/submucosa</td>
<td><strong>A</strong>: T3: through muscle wall</td>
<td><strong>A</strong>: T1-T2&lt;br&gt;N1/N1c&lt;br&gt;T1, N2a</td>
<td>Any T, Any N, M1a</td>
</tr>
<tr>
<td><strong>T2</strong>: invades muscularis propria</td>
<td><strong>B</strong>: T4a: penetrates visceral peritoneum</td>
<td><strong>B</strong>: T3 -T4a&lt;br&gt;N1/N1c&lt;br&gt;T2-T3, N2a&lt;br&gt;T1-T2, N2b</td>
<td>Any T, Any N, M1b</td>
</tr>
<tr>
<td><strong>C</strong>: T4b: invades or adherent to organs or structures</td>
<td><strong>C</strong>: T4a, N2a&lt;br&gt;T3-4a,N2b T4b, N1-N2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Metastatic CRC (mCRC) Treatment Schema

- Surgery and anastomosis or bypass of obstructing lesion
- Surgical resection of isolated metastases (e.g., liver, lung, ovaries)
- Palliative radiation therapy
- Chemotherapy ± monoclonal antibody
- Multikinase inhibitor
- Clinical trials evaluating new drugs, new drug combinations, or molecular therapies

### Key Therapeutic Agents in CRC: Historical Perspective

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>5-Fluorouracil (5-FU) approved</td>
</tr>
<tr>
<td>1998</td>
<td>Irinotecan as single agent approved as second-line treatment</td>
</tr>
<tr>
<td>2000</td>
<td>Irinotecan + 5-FU approved as first-line treatment</td>
</tr>
<tr>
<td>2001</td>
<td>Capecitabine approved as first-line treatment</td>
</tr>
<tr>
<td>2002</td>
<td>Oxaliplatin + 5-FU approved as second-line treatment</td>
</tr>
</tbody>
</table>
| 2004 | Approval of biologics  
  - Bevacizumab  
  - Cetuximab  
  - Approval of oxaliplatin in the adjuvant setting |
| 2005 | Approval of capecitabine in the adjuvant setting |
| 2006 | Approval of panitumumab |
| 2012 | Approval of ziv-aflibercept  
  - Approval of regorafenib |

# Commonly Used Agents for Treatment of mCRC

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoropyrimidines</td>
<td>5-Flourouracil</td>
</tr>
<tr>
<td></td>
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<td>VEGFR Inhibitors</td>
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</tr>
<tr>
<td>EGFR Inhibitors</td>
<td>Cetuximab</td>
</tr>
<tr>
<td></td>
<td>Panitumumab</td>
</tr>
<tr>
<td>Multikinase Inhibitors</td>
<td>Regorafenib</td>
</tr>
</tbody>
</table>

EGFR = epidermal growth factor receptor; VEGFR = vascular endothelial growth factor receptor.


**Irinotecan**

**FDA indication:**
- Indicated for patients with mCRC whose disease has recurred or progressed following initial fluorouracil-based therapy\(^1\)

**NCCN guidelines:**
- For treatment of mCRC in combination with 5-FU and leucovorin (FOLFIRI) ± bevacizumab, cetuximab or panitumumab (KRAS/NRAS WT only), ziv-aflibercept or as a single agent\(^2\)

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5-FU = 5-fluorouracil; FOLFIRI = irinotecan, leucovorin, and 5-fluorouracil; WT = wild type.

Capecitabine

- Efficacy equivalent to that of intravenous (IV) bolus 5-FU/leucovorin

**FDA indication:**
- Indicated as adjuvant therapy for patients with Duke’s C CRC (TNM stage III) or first-line treatment of mCRC when treatment with fluoropyrimidine alone is preferred

**NCCN guidelines:**
- Adjuvant therapy for stage III CRC single agent or in combination with oxaliplatin (CapeOx)
- mCRC single agent or in combination with oxaliplatin (CapeOx)

5-FU = 5-fluorouracil; CapeOx = capecitabine + oxaliplatin; CRC = colorectal cancer; TNM = tumor, node, metastasis.

Oxaliplatin

FDA indication:
- Indicated for adjuvant therapy for stage III CRC and treatment of advanced CRC in combination with 5-FU and leucovorin¹

NCCN guidelines²:
- Adjuvant therapy for stage III CRC in combination with 5-FU and leucovorin (FOLFOX or FLOX)
- For treatment of mCRC, FOLFOX ± bevacizumab, cetuximab or panitumumab (KRAS/NRAS WT only) or in combination with 5-FU, leucovorin, and irinotecan (FOLFOXIRI)

5-FU = 5-fluorouracil; FOLFOX = 5-fluorouracil + leucovorin + oxaliplatin; FOLFOXIRI = 5-fluorouracil + leucovorin + oxaliplatin + irinotecan; mCRC = metastatic colorectal cancer; WT = wild type.

Bevacizumab

FDA indication¹:
- Indicated for treatment of mCRC in combination with IV 5-FU–based chemotherapy for first- or second-line therapy, in combination with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin–based therapy
- Second-line treatment in patients with mCRC who progressed on a first-line bevacizumab-containing regimen

NCCN guidelines:
- For first- or second-line treatment of mCRC in combination with FOLFOX, CapeOx, FOLFIRI, 5-FU/leucovorin or capecitabine; for first-line treatment with FOLFOXIRI, for second-line treatment with irinotecan²

5-FU = 5-fluorouracil; CapeOx = capecitabine + oxaliplatin; FOLFIRI = irinotecan, leucovorin, and 5-fluorouracil; FOLFOX = 5-fluorouracil + leucovorin + oxaliplatin; FOLFOXIRI = 5-fluorouracil + leucovorin + oxaliplatin + irinotecan; mCRC = metastatic colorectal cancer.

Cetuximab

- Chimeric monoclonal antibody\(^1\)

**FDA indication\(^1\):**
- For patients with mCRC with *KRAS* WT gene only
- In combination with FOLFIRI for first-line treatment
- In combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy
- As a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or are intolerant to irinotecan

**NCCN guidelines\(^2\):**
- For treatment of mCRC in combination with FOLFIRI
- In combination with irinotecan or as a single agent (for patients intolerant to irinotecan) for therapy following first or second progression (*KRAS/NRAS WT only*)

FOLFIRI = irinotecan, leucovorin, and 5-fluorouracil; mCRC = metastatic colorectal cancer; WT = wild type.

Panitumumab

- Recombinant, human IgG2 kappa monoclonal antibody

**FDA indication**:  
- For mCRC patients with *KRAS* WT gene only  
- Indicated as a single agent for treatment of mCRC with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-based regimens

**NCCN guidelines**:  
- For treatment of mCRC in combination with FOLFOX, FOLFIRI, irinotecan, or as a single agent (*KRAS/NRAS* WT only)

FOLFIRI = irinotecan, leucovorin, and 5-fluorouracil; FOLFOX = 5-fluorouracil + leucovorin + oxaliplatin; mCRC = metastatic colorectal cancer; WT = wild type.

**KRAS** as a Predictive Marker for ANTI-EGFR Monoclonal Antibody Response

- *KRAS* is a gene that codes for a protein that plays an important role downstream of the EGFR in the signaling pathway.

- There are 2 different forms of the *KRAS* gene found in colorectal tumors:
  - Wild type (WT) (normal or nonmutated): approximately 60% of patients
  - Mutated (abnormal): approximately 40% of patients, with mutations occurring in exon 2

- In mutant *KRAS* tumors, the *KRAS* gene is constantly “turned on,” resulting in continuous signaling and cellular growth.

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KRAS Retrospective Data

- Results from phase II and III clinical trials have shown that select patients with mCRC benefit from treatment with an EGFR inhibitor as monotherapy or combined with chemotherapy.
- Retrospective subset analyses of the data from these pivotal trials strongly suggest that patients with KRAS mutations in codon 12 or 13 do not benefit from therapy (approximately 35%–45% of patients).
- Only patients with WT KRAS are appropriate candidates for treatment with EGFR inhibitor therapy.

ASCO Guidelines: 2009 Provisional Clinical Opinion (PCO) on KRAS Testing

- ASCO recommends that all patients with mCRC who are candidates for anti-EGFR antibody therapy have their tumors tested for KRAS gene mutations.
- It recommends against the use of anti-EGFR antibody therapy for patients with positive test results for the KRAS mutation in codons 12 or 13.
- Intended to preliminarily guide treatment with the anti-EGFR monoclonal antibodies cetuximab and panitumumab.

NCCN Guidelines: *KRAS* and *NRAS* Mutation Testing

- All patients with mCRC should have tissue genotyped for RAS mutations (KRAS and NRAS).
- Patients with any known KRAS mutation (exon 2 or non-exon 2) or NRAS mutations should not be treated with either cetuximab or panitumumab.

Regorafenib

**FDA indication:**
- For patients with mCRC previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *KRAS* WT, an anti-EGFR therapy\(^1\)

**NCCN guidelines:**
- As a single agent for patients with mCRC following first-line progression after initial treatment with FOLFOXIRI ± bevacizumab, or following second-line progression\(^2\)

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Dosing of Regorafenib

- **Recommended dose:** 160 mg daily (4 x 40 mg tablets)
- **Taken orally with a low-fat breakfast**
- **Treatment is 21 consecutive days followed by 7 days off therapy**
- **Hold treatment for:**
  - Recurrent grade 2 hand-foot skin reaction (HFSR) or grade 3 HFSR
  - Symptomatic grade 2 hypertension
  - Any grade 3 or 4 adverse event
- **Reduce dose for:**
  - Grade 2 HFSR
  - Grade 3 AST/ALT
  - Following recovery of any grade 3 or 4 adverse event

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HFSR = hand-foot skin reaction.

Ziv-Aflibercept

FDA indication:
- In combination with FOLFIRI, for mCRC that is resistant to or has progressed following treatment with an oxaliplatin-containing regimen

NCCN guidelines:
- For treatment of mCRC after first-line therapy progression, given in combination with FOLFIRI or irinotecan

FOLFIRI = irinotecan, leucovorin, and 5-fluorouracil; mCRC = metastatic colorectal cancer.

Dosing of Ziv-Aflibercept

- Recommended dose: 4 mg/kg as an IV infusion over 1 hour every 2 weeks
- Given in combination with FOLFIRI or irinotecan
- Hold drug:
  - ≥4 weeks prior to surgery
  - Recurrent or severe hypertension
  - Proteinuria of ≥2 g per 24 hours

Clinical Strategies for Selecting Optimal Therapy for mCRC

<table>
<thead>
<tr>
<th>Patient-specific considerations</th>
<th>Treatment-specific considerations</th>
<th>Quality of life considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prior treatments</td>
<td>• Biomarker assessment</td>
<td>• Insurance coverage</td>
</tr>
<tr>
<td>• Comorbidities</td>
<td>• Toxicity profile</td>
<td>• Complexity of regimen</td>
</tr>
<tr>
<td>• Performance status</td>
<td></td>
<td>• Access</td>
</tr>
</tbody>
</table>

Quality of life considerations

- Insurance coverage
- Complexity of regimen
- Access
- Caregiver support
- Lifestyle
Audience Question 1

- Does your institution adhere to practice guidelines in treatment decision-making?
For patients with mCRC appropriate for intensive therapy:

**Initial therapy**

- FOLFOX ± bevacizumab or
- CapeOx ± bevacizumab or
- FOLFOX ± cetuximab or panitumumab (*KRAS/NRAS WT* gene only) or
- FOLFIRI + bevacizumab or
- FOLFIRI ± cetuximab or panitumumab (*KRAS/NRAS WT* gene only) or
- 5-FU/leucovorin or capecitabine ± bevacizumab or
- FOLFOXIRI ± bevacizumab (category 2B)

5-FU = 5-fluorouracil; CapeOx = capecitabine + oxaliplatin; FOLFIRI = irinotecan, leucovorin, and 5-fluorouracil; FOLFOX = 5-fluorouracil + leucovorin + oxaliplatin; FOLFOXIRI = 5-fluorouracil + leucovorin + oxaliplatin + irinotecan; mCRC = metastatic colorectal cancer; WT = wild type.
For patients with mCRC appropriate for intensive therapy:

**Therapy after first-line progression**

- FOLFIRI ± bevacizumab or ± ziv-aflibercept or
- Irinotecan ± bevacizumab or ± ziv-aflibercept or
- FOLFIRI + cetuximab or panitumumab (KRAS/NRAS WT gene only) or
- Irinotecan ± cetuximab or panitumumab (KRAS/NRAS WT gene only) or
- FOLFOX or CapeOx ± bevacizumab or
- Single-agent cetuximab or panitumumab (KRAS/NRAS WT gene only) in patients not able to tolerate combination
- Regorafenib (only for progression after initial treatment with FOLFOXIRI ± bevacizumab)

CapeOx = capecitabine + oxaliplatin; FOLFIRI = irinotecan, leucovorin, and 5-fluorouracil; FOLFOX = 5-fluorouracil + leucovorin + oxaliplatin; mCRC = metastatic colorectal cancer; WT = wild type.
NCCN mCRC Treatment Guideline Summary

For patients with mCRC appropriate for intensive therapy:

Therapy after second-line progression

- Cetuximab or panitumumab (*KRAS/NRAS* WT gene only) + irinotecan; for patients not able to tolerate combination, consider single-agent cetuximab or panitumumab (*KRAS/NRAS* WT gene only)
- FOLFOX or
- CapeOx or
- Regorafenib or
- Clinical trial or
- Best supportive care

CapeOx = capecitabine + oxaliplatin; FOLFOX = 5-fluorouracil + leucovorin + oxaliplatin; mCRC = metastatic colorectal cancer; WT = wild type.
NCCN mCRC Treatment Guideline Summary

For patients with mCRC appropriate for intensive therapy:

**Therapy after third-line progression**

- Regorafenib (if not given previously) or
- Clinical trial or
- Best supportive care
For patients with mCRC not appropriate for intensive therapy:

**Initial therapy**

- Capecitabine ± bevacizumab or
- Infusional 5-FU + leucovorin or
- Cetuximab (*KRAS/NRAS* WT gene only) (category 2B) or
- Panitumumab (*KRAS/NRAS* WT gene only) (category 2B)

5-FU = 5-fluorouracil; mCRC = metastatic colorectal cancer; WT = wild type.
NCCN mCRC Treatment Guideline Summary

For patients with mCRC not appropriate for intensive therapy:

**Following Initial Therapy**

- **Improved Functional Status**: Consider initial therapy for mCRC
- **No Improvement in Functional Status**: Best supportive care

ASCO 2014: First-line Biologic Agents Show Equivalent Results in mCRC

- Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy + Cetuximab (N = 578)</td>
<td>10.45</td>
<td>29.94</td>
</tr>
<tr>
<td>Chemotherapy + Bevacizumab (N= 559)</td>
<td>10.83</td>
<td>29.03</td>
</tr>
</tbody>
</table>

PFS = progression free survival; OS = overall survival
Venook AP, et al. J Clin Oncol. 32:5s, 2014 (suppl; abstr LBA3)
Patient Care Considerations
mCRC Treatment

Myelosuppression

Integumentary

Vascular

Pulmonary

Genitourinary

Neurotoxicity

Gastrointestinal

Infusion Reaction

Graphic courtesy of Carolyn Grande, CRNP, AOCNPc
Commonly Used Agents for Treatment of mCRC

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<td>Panitumumab</td>
</tr>
<tr>
<td>Multikinase Inhibitors</td>
<td>Regorafenib</td>
</tr>
</tbody>
</table>
## Side Effects of mCRC Treatment

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Irinotecan&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Capecitabine&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Oxaliplatin&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>X</td>
<td>X*</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>X</td>
<td>X*</td>
<td>X</td>
</tr>
<tr>
<td>Cholinergic Symptoms</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand-Foot Syndrome</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Hypersensitivity Reaction</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

*In US increased incidence of grade ¾ events.<sup>4</sup>

# Side Effects of EGFR Inhibitors in mCRC Treatment

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Cetuximab(^1)</th>
<th>Panitumumab(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>X (3%)</td>
<td>X (1%)</td>
</tr>
<tr>
<td>Papulopustular rash</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
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# Side Effects of VEGFR Inhibitors and Multikinase Inhibitors in mCRC Treatment

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Bevacizumab&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Ziv-aflibercept&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Regorafenib&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Epistaxis/bleeding</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Gastrointestinal perforation</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Delayed wound healing</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Cardiac ischemia/infarction</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Arterial thrombotic event</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fistulae</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

## Acute or Delayed Diarrhea Related to Irinotecan

<table>
<thead>
<tr>
<th>Acute</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cholinergic mechanism during or shortly after irinotecan infusion</td>
<td>• Occurring &gt;24 hours after an irinotecan infusion</td>
</tr>
<tr>
<td>• Symptoms: rhinitis, increased salivation, flushing, diaphoresis, intestinal abdominal cramping</td>
<td>• Should be managed immediately with loperamide</td>
</tr>
<tr>
<td>• Treatment: prophylactic or therapeutic administration of atropine 0.25–1 mg IV or SC</td>
<td>• Patients should be carefully monitored for dehydration and electrolyte imbalances</td>
</tr>
</tbody>
</table>
### Comprehensive Diarrhea Assessment

<table>
<thead>
<tr>
<th>Comprehensive History</th>
<th>Patient Report</th>
<th>Dehydration Evaluation</th>
<th>Physical Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Review of complete medication list including medications stopped within the last month: laxatives, opioids, antibiotics, regular and as-needed medications, herbal and over-the-counter medications, vitamins and supplements, chemotherapy and biotherapy agents</td>
<td>- Description of baseline and current bowel movements</td>
<td>- Objective assessment: assess orthostatic hypotension, weight loss, skin turgor, dry mucous membranes</td>
<td>- Palpate abdomen for tenderness Percuss – dullness may indicate obstruction or fecal impaction</td>
</tr>
<tr>
<td></td>
<td>- Probe for specifics including: when change in patterns began; frequency, amount, consistency, and color of stool; incontinence episodes; presence of blood in stool and distinct odor associated with stool</td>
<td>- Subjective assessment: dizziness, weakness, excessive thirst, decreased urination</td>
<td>- Ascultate for bowel sounds</td>
</tr>
</tbody>
</table>
# Common Terminology Criteria for Adverse Events (CTCAE) Reporting: Diarrhea

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhea</strong></td>
<td>Increase of &lt;4 stools per day over baseline; mild increase in ostomy output compared with baseline</td>
<td>Increase of 4–6 stools per day over baseline; moderate ostomy output compared with baseline</td>
<td>Increase of ≥7 stools per day; incontinence; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care activities of daily living (ADLs)</td>
<td>Life-threatening consequence; urgent intervention needed</td>
<td>Death</td>
</tr>
</tbody>
</table>

*Note.* Based on information from the National Cancer Institute, 2009. A semi-colon indicates “or” in the grade description.

Management of mCRC Treatment-Induced Diarrhea

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Pharmacologic Intervention</th>
<th>Nonpharmacologic Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1−2 diarrhea</td>
<td>• Loperamide: initial dose 4 mg followed by 2 mg every 4 hours or after every unformed stool</td>
<td>• Stop all caffeine or lactose-containing products, alcohol, and high-osmolar supplements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Drink 64−100 oz of liquids a day (sports drink with electrolytes or broth)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Eat frequent, small meals of bananas, rice, applesauce, toast (BRAT diet) or plain pasta</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If grade 2, hold cytotoxic chemotherapy until symptoms resolve and consider dose reduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess 12−24 hours later: diarrhea improving</td>
<td>• Discontinue loperamide after 12-hour diarrhea-free interval</td>
<td>• Continue dietary modification</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Gradually add solid</td>
</tr>
<tr>
<td>Assess 12−24 hours later: diarrhea not improving</td>
<td>Diarrhea remains grades 1−2:</td>
<td>Diarrhea remains grades 1−2:</td>
</tr>
<tr>
<td></td>
<td>• Continue loperamide 2 mg every 2 hours</td>
<td>• Continue with current dietary restrictions</td>
</tr>
<tr>
<td></td>
<td>• Start oral antibiotics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea progresses to grades 3−4:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Admit to the hospital</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Initiate octreotide 100−150 μg SC 3 times daily or IV 25−50 mg/h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Start IV fluids and antibiotics as needed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Stool evaluation, CBC, and electrolyte levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Discontinue cytotoxic chemotherapy until all symptoms resolve, restart at reduced dose</td>
<td></td>
</tr>
</tbody>
</table>
Neurotoxicity: Acute

• Usually occurs during or immediately after oxaliplatin infusion
• Precipitated by exposure to cold temperature and contact with cold objects
• Usually transient and occurs in ~90% of patients receiving oxaliplatin
• Reported symptoms include:
  – Jaw tightness or spasm
  – Tightness in the back of the throat
  – Chest pressure
  – Dysarthria
  – Eye pain
  – Abnormal tongue sensation
• Resolves within 14 days but can occur with subsequent treatments
Neurotoxicity: Cumulative

- Usually occurs later in treatment
- Generally seen after cumulative dosing of >750–850 mg/m²
- Can persist between cycles, and increases in intensity with higher cumulative doses
- Patients may describe impaired sensation with hand-foot numbness or tingling
- Patients may have difficulty walking or feeling the gas pedal due to impaired proprioception
- Can be significant enough to interfere with activities of daily living (ADL)
- Consistently reversible, with most patients recovering from grade 3 neurotoxicity to grade 1 within 6 to 12 months of discontinuing therapy

Neurotoxicity: Management Strategies

- Education of patients and caregivers is crucial\(^1\)
- Conduct a baseline neuropathy assessment\(^2\)
- Instruct patients to avoid direct exposure to cold objects, cold environments, and cold liquids\(^1\)
- Provide reassurance that the acute symptoms of oxaliplatin-induced neurotoxicity is transient\(^1\)
- Assessment should involve questioning the patient regarding the nature of their symptoms, including location, duration, and severity\(^1\)
- Caution patients regarding the need to institute safety measures in their homes\(^3\)
- For most patients, cumulative oxaliplatin-associated peripheral neuropathy is reversible\(^1\)

## Compare and Contrast: Hand-Foot Syndrome (HFS) and Hand-Foot Skin Reaction (HFSR)

<table>
<thead>
<tr>
<th>HFS</th>
<th>HFSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A cutaneous complication seen in patients receiving fluorouracil</td>
<td>• Has been shown to occur in anywhere from 9% to 62% of patients on</td>
</tr>
<tr>
<td>therapy, capecitabine, and liposomal doxorubicin¹</td>
<td>multikinase inhibitors³</td>
</tr>
<tr>
<td>• Similarities to HFSR include erythema, blisters, and effects on</td>
<td>• Can develop within the first 2–4 weeks of treatment³,⁴</td>
</tr>
<tr>
<td>the palms of the hands and soles of the feet¹</td>
<td>• Lesions can be tender and initially may appear with a peripheral</td>
</tr>
<tr>
<td>• The typical pattern of localized hyperkeratotic lesions surrounded</td>
<td>halo of erythema localized at pressure areas³</td>
</tr>
<tr>
<td>by erythematous areas distinguishes HFSR from HFS. Subjective</td>
<td>• Similar developments can be identified on the distal phalanges and</td>
</tr>
<tr>
<td>symptoms of HFSR include paresthesia, burning, pain, and decreased</td>
<td>the fingertips, particularly around the nails²</td>
</tr>
<tr>
<td>tolerance to heat²</td>
<td>• After several weeks, the lesions (with or without blisters) are</td>
</tr>
<tr>
<td></td>
<td>followed by thickened, hyperkeratotic skin (calluses) that can be</td>
</tr>
<tr>
<td></td>
<td>painful and impair ADLs³,⁴</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFSR</td>
<td>Minimal skin changes or dermatitis (eg, erythema, edema, or hyperkeratosis) without pain</td>
<td>Skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADLs</td>
<td>Severe skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADLs</td>
</tr>
</tbody>
</table>

Classic HFSR

Halo of erythema

Hyperkeratotic/ hyperpigmented area on metacarpo-phalangeal joint

Thickened hyperkeratotic skin on pressure area
## HFSR Prevention and Management

### Prevention

- Examination of the skin with emphasis on hyperkeratotic areas on palms and soles\(^1\)
- Patients can receive a pedicure by a podiatrist to remove any preexisting hyperkeratotic areas or calluses that may reduce the exposure of their hands and feet to hot water\(^1\)
- Avoid constrictive footwear\(^1\)
- Avoid excessive friction on the skin when applying lotion, during massages, or in the process of everyday tasks, such as typing\(^1\)
- Avoid vigorous exercise or activities that place undue stress on the hands and feet, especially during the first month\(^1\)
- Wear thick cotton gloves or socks to prevent injury and keep palms and soles dry\(^1\)
- Wear shoes with padded insoles to reduce pressure on the feet\(^1\)
- Apply salicylic acid and/or urea-containing lotion twice daily to help with natural exfoliation and chemical debridement of hyperkeratotic areas, such as calluses\(^1,2\)

### Management

- No prospective, randomized trials have been undertaken to determine the best management strategy for HFSR\(^1,2\)
- No evidence-based national clinical guidelines are currently available

Treatment Modifications of Regorafenib for CTCAE Grade 2 or 3 HFSR

- **Reduce dose to 120 mg:**
  - For the first occurrence of grade 2 HFSR of any duration

- **Reduce dose to 80 mg:**
  - For recurrence of grade 2 HFSR at the 120 mg dose

- **Hold treatment:**
  - NCI CTCAE grade 2 HFSR that is recurrent or does not improve within 7 days despite dose reduction
  - Interrupt therapy for a minimum of 7 days for grade 3 HFSR
# Papulopustular Rash: Prophylaxis

<table>
<thead>
<tr>
<th>MASCC(^1)</th>
<th>NCCN(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Minocycline 100 mg daily or doxycycline 100 mg twice daily</td>
<td>• Oral semisynthetic tetracycline agents (doxycycline or minocycline)</td>
</tr>
<tr>
<td>• Hydrocortisone 1% cream with moisturizer and sunscreen twice daily</td>
<td>• Doxycycline 100 mg twice daily in combination with hydrocortisone 1%, skin moisturizer, and sunscreen(^2)</td>
</tr>
</tbody>
</table>

MASCC = Multinational Association for Supportive Care in Cancer; NCCN = National Comprehensive Cancer Network.

**Papulopustular Rash: Treatment**

<table>
<thead>
<tr>
<th>MASCC¹</th>
<th>NCCN²</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Alclometasone 0.05% cream</td>
<td>• Topical steroids and antibiotics, such as clindamycin and erythromycin</td>
</tr>
<tr>
<td>• Fluocinonide 0.05% cream twice daily</td>
<td>• Oral antibiotics: doxycycline or minocycline (based on anecdotal or nonrandomized studies)</td>
</tr>
<tr>
<td>• Clindamycin 1%</td>
<td>• Systemic steroids are not typically used</td>
</tr>
<tr>
<td>• Doxycycline 100 mg twice daily</td>
<td>• Isotretinoin reactively (based on anecdotal or nonrandomized studies)</td>
</tr>
<tr>
<td>• Minocycline 100 mg daily</td>
<td></td>
</tr>
<tr>
<td>• Isotretinoin at low doses of 20–30 mg/day</td>
<td></td>
</tr>
</tbody>
</table>

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Papulopustular Rash: Prevention and Treatment

• Regular use of thick, alcohol-free moisturizers is recommended to minimize skin irritation

• Application of sunscreen with sun protective factor of ≥15 every morning and prior to direct sun exposure will protect skin from the increased sun sensitivity

• Sensitivity to sunlight may also be exacerbated by some antibiotics (specifically tetracyclines, which may be used to reduce inflammation)

• For pruritis, oral antihistamines

Hypertension

- Hypertension is one of the most common side effects of antiangiogenic and VEGF inhibitor therapies
- It can occur in patients being treated with any VEGF inhibitor despite the mechanism of action
- New JNC 8 guidelines for diagnosis and management of hypertension are appropriate for VEGF-induced hypertension
- Hypertension is often easily managed with a thiazide-type diuretic, a beta-blocker, an angiotensin-converting enzyme inhibitor, or an angiotensin receptor blocker, alone or in combination
Audience Questions

- How many of you treat hypertension related to VEGFR inhibitors or multikinase inhibitors?
- If you are not treating hypertension, are you referring your patients to their primary care physician or a cardiologist?
# Hypertension Management

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>Systolic mm Hg</th>
<th>Diastolic mm Hg</th>
<th>Lifestyle Modification</th>
<th>Initial Drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>and &lt;80</td>
<td>Encourage</td>
<td></td>
</tr>
<tr>
<td>Pre-HTN</td>
<td>120–139</td>
<td>or 80–89</td>
<td>Yes</td>
<td>No antihypertensive drug indicated</td>
</tr>
<tr>
<td>Stage 1 HTN</td>
<td>140–159</td>
<td>or 90–99</td>
<td>Yes</td>
<td>Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination</td>
</tr>
<tr>
<td>Stage 2 HTN</td>
<td>≥160</td>
<td>or ≥ 100</td>
<td>Yes</td>
<td>2-drug combination for most (usually thiazide-type diuretic and ACEI or ARB, BB, or CCB)</td>
</tr>
</tbody>
</table>

BP = blood pressure; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta blocker; CCB calcium channel blocker; HTN = hypertension.
Hypertension Management With VEGFR Inhibitors and Multikinase Inhibitors

**Bevacizumab**
- Monitor blood pressure (BP) every 2–3 weeks during treatment with bevacizumab
- Treat with appropriate antihypertensive therapy and monitor BP regularly
- Temporarily suspend bevacizumab in patients with severe hypertension that is not controlled with medical management
- Discontinue bevacizumab in patients with hypertensive crisis or hypertensive encephalopathy
- Continue to monitor BP at regular intervals in patients with bevacizumab-induced or -exacerbated hypertension after discontinuation of bevacizumab

**Ziv-aflibercept**
- Monitor BP every 2 weeks or more frequently as indicated during treatment
- Treat with appropriate antihypertensive therapy and continue monitoring BP
- Temporarily suspend ziv-aflibercept in patients with uncontrolled hypertension until controlled, and permanently reduce ziv-aflibercept dose to 2 mg/kg for subsequent cycles
- Discontinue treatment in patients with hypertensive crisis or hypertensive encephalopathy

**Regorafenib**
- Do not initiate regorafenib unless blood pressure is adequately controlled
- Monitor blood pressure weekly for the first 6 weeks of treatment and then every cycle, or more frequently, as clinically indicated
- Temporarily or permanently withhold regorafenib for severe or uncontrolled hypertension

Hepatotoxicity: CTCAE Grading of Transaminases

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT &gt;ULN - 3.0 x ULN</td>
<td>&gt;3.0 - 5.0 x ULN</td>
<td>&gt;5.0 - 20.0 x ULN</td>
<td>&gt;20.0 x ULN</td>
</tr>
<tr>
<td>AST &gt;ULN - 3.0 x ULN</td>
<td>&gt;3.0 - 5.0 x ULN</td>
<td>&gt;5.0 - 20.0 x ULN</td>
<td>&gt;20.0 x ULN</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

Monitoring and Management of Patients With Hepatotoxicity on Regorafenib

- Obtain liver function tests (ALT, AST, and bilirubin) prior to initiation of treatment with regorafenib
- Monitor at least every 2 weeks during the first 2 months of treatment
- Following 2 months of treatment, monitor monthly or more frequently as clinically indicated
- Reduce the dose of regorafenib to 120 mg:
  - For grade 3 AST/ALT elevation
  - Resume only if the potential benefit outweighs the risk of hepatotoxicity
  - Discontinue use of regorafenib for:
    - Any occurrence of AST or ALT >20 times the ULN
    - Any occurrence of AST or ALT >3 times the ULN with concurrent bilirubin >2 times the ULN
    - Recurrence of AST or ALT >5 times the ULN despite dose reduction to 120 mg

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.
mCRC Treatment Summary

- From 1998 through 2006, an influx of new agents with various mechanisms of action was introduced into the armamentarium of treatment options for patients with mCRC
- This explosion led to further research on optimally sequencing, combining, and predicting which agents would be most efficacious for a patient with mCRC
- Thorough assessment and management of treatment-related toxicities is critical in enabling patients with mCRC to continue on the most efficacious dosing and schedule of their prescribed therapy