# Chapter 61: Colorectal Cancer

## INTRODUCTION

- *Colorectal cancer* (CRC) is a malignant neoplasm involving the colon, rectum, and anal canal.

## PATHOPHYSIOLOGY

- Development of a colorectal neoplasm is a multistep process of genetic and phenotypic alterations of normal bowel epithelium structure and function leading to dysregulated cell growth, proliferation, and tumor development.
- Features of colorectal tumorigenesis include genomic instability, activation of oncogene pathways, mutational inactivation or silencing of tumor-suppressor genes, DNA mismatch repairs, and activation of growth factor pathways.
- Adenocarcinomas account for about 92% of tumors of the large intestine.

## PREVENTION AND SCREENING

- *Primary prevention* is aimed at preventing CRC in an at-risk population. Trials with celecoxib in people with familial adenomatous polyposis (FAP) showed reduction in size and number of polyps after 6–9 months of treatment, but there is a lack of long-term benefit.
- *Secondary prevention* is aimed at preventing malignancy in a population that has already manifested an initial disease process. Secondary prevention includes procedures ranging from colonoscopic removal of precancerous polyps detected during screening colonoscopy to total colectomy for high-risk individuals (eg, FAP).
- Current US guidelines for average-risk individuals include annual occult fecal blood testing starting at age 50 years and examination of the colon every 5 or 10 years, depending on the procedure.

## CLINICAL MANIFESTATIONS

- Signs and symptoms of CRC can be extremely varied, subtle, and nonspecific. Early-stage CRC is often asymptomatic and detected by screening procedures.
- Blood in the stool is the most common sign; however, any change in bowel habits, vague abdominal discomfort, or abdominal distention may be a warning sign. Less common signs and symptoms include nausea, vomiting, and, if anemia is severe, fatigue.
- Twenty percent of patients present with metastatic disease most commonly in the liver, lung, and bones.

## DIAGNOSIS

- Perform a physical examination and obtain a careful personal and family history. Evaluate entire large bowel by colonoscopy.
- Obtain baseline laboratory tests: complete blood cell count, international normalized ratio (INR), activated partial thromboplastin time, liver and renal function tests, and serum carcinoembryonic antigen (CEA). Serum CEA serves as a marker for monitoring CRC response to treatment, but it is too insensitive and nonspecific to be used as a screening test for early-stage CRC.
- Radiographic imaging studies may include chest radiographs, bone scan, chest and abdominal computed tomography scans, positron emission

tomography, ultrasonography, and magnetic resonance imaging.

- Determine CRC stage at diagnosis to predict prognosis and develop treatment options. Stage is based on size of the primary tumor ($T_{1–4}$), presence and extent of lymph node involvement ($N_{0–2}$), and presence or absence of distant metastases (M).

  ✔ Stage I disease involves tumor invasion of the submucosa ($T_1$) or muscularis propria ($T_2$) and negative lymph nodes.

  ✔ Stage II disease involves tumor invasion through the muscularis propria into pericolorectal tissues ($T_3$), or penetration to the surface of the visceral peritoneum ($T_{4a}$), or directly invades or is adherent to other organs or structures ($T_{4b}$), and negative lymph nodes.

  ✔ Stage III disease includes $T_{1–4}$ and positive regional lymph nodes.

  ✔ Stage IV disease includes any T, any N, and distant metastasis.

## PROGNOSIS

- Stage at diagnosis is the most important independent prognostic factor for survival and disease recurrence. Five-year relative survival is approximately 90% for those with localized tumor as compared with 14% for those with metastatic disease at diagnosis.
- Poor prognostic clinical factors at diagnosis include bowel obstruction or perforation, high preoperative CEA level, distant metastases, and location of the primary tumor in the rectum or rectosigmoid area.
- Molecular markers, particularly MSI, 18q/*DCC* mutation or LOH, *BRAF V600E* mutation, and *RAS* mutations are also associated with CRC prognosis.

## TREATMENT

- Goals of Treatment: The goals include cure for stages I, II, and III; the intent is to eradicate micrometastatic disease after surgical resection. Most stage IV disease is incurable; palliative treatment is given to reduce symptoms, avoid disease-related complications, and prolong survival. Twenty to 30% of patients with metastatic disease may be cured if their metastases are resectable.
- Treatment modalities are surgery, radiation therapy (RT), chemotherapy, and biomodulators.

### Operable Disease

#### Surgery

- Complete surgical resection of the primary tumor with regional lymphadenectomy is a curative approach for patients with operable CRC.
- The preferred surgical procedure for rectal cancer is a total excision of the mesorectum that includes tissue containing perirectal fat and draining lymph nodes.
- infection, anastomotic leakage, obstruction, adhesions, sexual dysfunction, and malabsorption syndromes.

#### Adjuvant Radiation Therapy

- Adjuvant RT has a limited role in colon cancer because most recurrences are extrapelvic and occur in the abdomen.

#### Adjuvant Chemotherapy for Colon Cancer

- Adjuvant therapy is administered after complete tumor resection to eliminate residual micrometastatic disease. Adjuvant therapy is not indicated for stage I CRC because more than 90% of patients are cured by surgical resection alone.
- Results of adjuvant chemotherapy studies in patients with stage II disease are conflicting. Despite a lack of consensus among practitioners, the

approach to treatment of high-risk stages II and III disease is similar.

- Adjuvant chemotherapy is the standard of care for stage III colon cancer.
- Standard adjuvant regimens include a fluoropyrimidine (**fluorouracil** [with **leucovorin**] or **capecitabine**) as a single agent or in combination with **oxaliplatin**. Leucovorin enhances cytotoxic activity of fluorouracil.
- Administration method affects clinical activity and toxicity. In most common combination regimens, fluorouracil is administered by both IV bolus injection and by continuous IV infusion. No one treatment schedule is superior for overall patient survival.
- Continuous IV infusion of fluorouracil is generally well tolerated but is associated with palmar-plantar erythrodysesthesia (hand–foot syndrome) and stomatitis. IV bolus administration is associated with leukopenia, which is dose limiting and can be life threatening. Both administration methods are associated with a similar incidence of mucositis, diarrhea, nausea and vomiting, and alopecia.
- In rare cases, patients deficient in dihydropyrimidine dehydrogenase, responsible for the catabolism of fluorouracil, develop severe toxicity, including death, after fluorouracil administration.
- National guidelines recommend oxaliplatin-based regimens as the first-line option for patients with stage III colon cancer who can tolerate combination therapy. It is commonly administered with fluorouracil/leucovorin. Oxaliplatin is associated with both acute and persistent neuropathies, including rare, acute pharyngolaryngeal dysesthesia, neutropenia, and gastrointestinal (GI) toxicity.
- Selection of an adjuvant regimen (**Table 61-1**) is based on patient-specific factors, including performance status, comorbid conditions, and patient preference based on lifestyle factors. Age should also be considered as subset analysis of large clinical trials has shown that patients older than 70 years may not benefit from adjuvant oxaliplatin.
- Fluorouracil/leucovorin regimens currently have limited use but are acceptable options in patients who cannot receive oxaliplatin and are unable to tolerate oral capecitabine.

TABLE 61-1

**Chemotherapy Regimens for the Adjuvant Treatment of Colorectal Cancer**

| Regimen | Agents | Comments |
|---|---|---|
| FOLFOX | Oxaliplatin 85 mg/m$^2$ IV on day 1<br>Leucovorin 400 mg/m$^2$ IV on day 1<br>Fluorouracil 400 mg/m$^2$ IV bolus, after leucovorin on day 1, then 1200 mg/m$^2$/day × 2 days CIV (total 2400 mg/m$^2$ over 46–48 hours)<br>Repeat every 2 weeks × 24 weeks[a] | Preferred regimen for stage III colon and rectal cancers; common toxicities: sensory neuropathy, neutropenia. |
| CapeOx | Oxaliplatin 130 mg/m$^2$ IV day 1<br>Capecitabine 1000 mg/m$^2$ twice daily orally days 1 through 14<br>Each cycle lasts 3 weeks × 24 weeks[b] | Improved DFS in patients with stage III colon cancer compared to capecitabine alone or Roswell Park Regimen; common dose-limiting toxicities: neuropathies and hand–foot syndrome. A preferred regimen for adjuvant rectal therapy. |
| Capecitabine | Capecitabine 1000 mg/m$^2$–1250 mg/m$^2$ PO twice daily on days 1 through 14<br>Each cycle lasts 14 days and is repeated every 3 weeks × 24 weeks | Equivalent DFS as compared with the Mayo Clinic regimen with improved tolerability; hand–foot syndrome common, useful for patients without vascular access or who have difficulties with travel to infusion center |
| Roswell Park Regimen | Leucovorin 500 mg/m$^2$ IV day 1 over 2 hours<br>Fluorouracil 500 mg/m$^2$ IV bolus 1 hour after leucovorin<br>Repeat weekly for 6 of 8 weeks × 4 cycles | Leukopenia common dose-limiting toxicity; diarrhea, and stomatitis common |
| Simplified Biweekly | Leucovorin 400 mg/m$^2$ per day IV<br>Fluorouracil 400 mg IV bolus, after leucovorin, then 1200 mg/m$^2$/day days 1 and 2 (total 2400 mg/m$^2$ over 46–48 hours) for 2 consecutive days<br>Repeat every 2 weeks × 12 cycles | Hand–foot syndrome common |

[a]Known as mFOLFOX6; survival benefit has not been demonstrated for patients 70 years and older.

[b]In patients with low-risk stage III (T1-3, any N), 3 months of CapeOX is noninferior to 6 months of CapeOX for DFS but this has not been proven for FOLFOX. In patients with high-risk stage III disease (T4, N1-2, or any T, N2), 3 months of FOLFOX is inferior to 6 months of FOLFOX for DFS, but this has not been proven with CapeOX. Grade 3 neuropathy is lower with 3 months of CapeOX or FOLFOX.

CIV, continuous intravenous infusion; DFS, disease-free survival; OS, overall survival; PO, by mouth.

### Adjuvant Therapy for Rectal Cancer

- Rectal cancer is more difficult to resect with wide margins, so local recurrences are more frequent than with colon cancer. Adjuvant RT plus chemotherapy is considered the standard of care for stages II and III rectal cancer.

- RT reduces the risk of local tumor recurrence in patients undergoing surgery for rectal cancer. RT is given prior to surgery to decrease tumor size, making it more resectable.
- Preoperative (neoadjuvant) chemoradiation shrinks rectal tumors prior to surgical resection, improving sphincter preservation. Preoperative infusional fluorouracil-based regimens or oral capecitabine plus RT are recommended. Patients should receive adjuvant chemotherapy following surgery to total 6 months of chemotherapy.

## Metastatic Disease

- Patients with metastatic colorectal cancer (MCRC) are considered to have resectable, potentially resectable, or unresectable metastatic disease. Surgery and RT are used to manage isolated sites of tumor. Chemotherapy is used for disseminated disease and is the primary treatment modality for unresectable MCRC.
- Tumor *RAS* (*KRAS* exon 2 and nonexon 2 and *NRAS*) and *BRAF* genotyping for mutation status and determination of tumor methylation or mismatch repair (MMR) or microsatellite instability (MSI) status (if not previously done) are recommended when metastatic disease is diagnosed to identify appropriate treatment options.

### Resectable or Potentially Resectable MCRC

- Surgical resection of metastases with curative intent is the primary goal.
- Neoadjuvant or conversional chemotherapy is administered to increase complete resection rates with resectable and potentially resectable liver or lung lesions (**Table 61-2**). Chemotherapy with or without biologic agents is given over 2–3 months pre-op. Adjuvant (postoperative) chemotherapy is administered to complete a total of 6 months of chemotherapy.
- Consider hepatic-directed therapy in addition to or as an alternative to surgical resection in patients with liver-only or liver-predominant MCRC. Hepatic artery infusion (HAI) delivers chemotherapy (eg, **floxuridine** and fluorouracil) through the hepatic artery directly into the liver. Tumor ablation uses radiofrequency ablation or microwave energy to generate heat to destroy tumor cells. Cryoablation is also used. These strategies are less successful than surgical interventions.

TABLE 61-2

**Initial Chemotherapeutic Regimens for Metastatic Colorectal Cancer**[a]

| Regimen | Agents | Major Dose-Limiting Toxicities | Comments |
|---|---|---|---|
| **Patients Appropriate for Intensive Therapy with *RAS* Mutations** | | | |
| FOLFOX ± bevacizumab | Oxaliplatin 85 mg/m$^2$ IV day 1<br>Leucovorin 400 mg/m$^2$ IV day 1<br>Fluorouracil 400 mg/m$^2$ IV bolus, after leucovorin day 1, then 1200 mg/m$^2$/day × 2 days CIV (total 2400 mg/m$^2$ over 46–48 hours)<br>Repeat every 2 weeks<br>± Bevacizumab 5 mg/kg IV | FOLFOX: sensory neuropathy, neutropenia<br>Bevacizumab: hypertension, thrombosis, proteinuria | Most commonly used first-line regimen |

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| | day 1 before FOLFOX<br>Repeat cycle every 2 weeks | | |
| CapeOx ± bevacizumab | Oxaliplatin 130 mg/m$^2$ IV day 1<br>Capecitabine 1000 mg/m$^2$ orally twice a day, days 1–14<br>Repeat cycle every 3 weeks<br>± Bevacizumab 7.5 mg/kg IV day 1<br>Repeat cycle every 3 weeks | CapeOx: diarrhea, hand–foot syndrome, neuropathies<br>Bevacizumab: hypertension, thrombosis, proteinuria | Reduced capecitabine dose better tolerated; patient must be able to be adherent and report side effects in a timely fashion |
| FOLFIRI ± bevacizumab | Irinotecan 180 mg/m$^2$ IV day 1<br>Leucovorin 400 mg/m$^2$ IV day 1<br>Fluorouracil 400 mg/m$^2$ IV bolus, after leucovorin day 1, then 1200 mg/m$^2$/day × 2 days CIV (total 2400 mg/m$^2$ over 46–48 hours)<br>± Bevacizumab 5 mg/kg IV day prior to FOLFIRI<br>Repeat cycle every 2 weeks | FOLFIRI: diarrhea, mucositis, neutropenia<br>Bevacizumab: hypertension, thrombosis, proteinuria | May be preferred in patients who have preexisting neuropathy or those in which neuropathy may be debilitating to their line of work (eg, musician) |
| Fluorouracil/Leucovorin ± bevacizumab | See Table 61-1 for fluorouracil/leucovorin regimen options<br>± Bevacizumab 5 mg/kg IV day prior to fluorouracil and leucovorin<br>Repeat cycle every 2 weeks | Fluorouracil/Leucovorin: diarrhea, hand–foot syndrome, mucositis, neutropenia<br>Bevacizumab: hypertension, thrombosis, proteinuria | Infusional fluorouracil/leucovorin regimen preferred to bolus fluorouracil regimen. Infusional regimens tend to have more hand–foot syndrome and stomatitis and bolus regimens more neutropenia; weekly or bimonthly schedule of leucovorin plus fluorouracil (either bolus or continuous infusion) may be more convenient for the patient in terms of fewer scheduled clinic appointments, less interference with work schedules, and ease of dose adjustments based on toxicity |
| Capecitabine ± bevacizumab | Capecitabine 850–1250 mg/m$^2$ orally twice a day, days 1–14<br>± Bevacizumab 7.5 mg/kg IV day 1<br>Repeat cycle every 3 weeks | Capecitabine: hand–foot syndrome, diarrhea, hyperbilirubinemia<br>Bevacizumab: hypertension, thrombosis, proteinuria | May be preferred in those without a port or limited venous access; patient must be able to be adherent and report side effects in a timely fashion |

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| FOLFOXIRI ± bevacizumab | Irinotecan 165 mg/m$^2$ IV day 1 prior to oxaliplatin<br>Oxaliplatin 85 mg/m$^2$ IV prior to leucovorin day 1<br>Leucovorin 400 mg/m$^2$ IV day 1 prior to fluorouracil<br>Fluorouracil 1200 mg/m$^2$/day × 2 days CIV (total 2400 mg/m$^2$ over 48 hours)[b]<br>Repeat cycle every 2 weeks<br>± Bevacizumab 5 mg/kg IV day 1 before FOLFOXIRI<br>Repeat cycle every 2 weeks | FOLFOXFIRI: neutropenia, diarrhea, stomatitis, peripheral neurotoxicity, thrombocytopenia<br>Bevacizumab: hypertension, thrombosis, proteinuria | More neutropenia and peripheral neurotoxicity compared to FOLFIRI; often used in medically fit individuals with diffuse aggressive disease to palliate symptoms and as potential conversion therapy |
| **Patients Appropriate for Intensive Therapy with *RAS* or *BRAF* Wild-Type and Left-Sided Tumors** | | | |
| FOLFOX + cetuximab or panitumumab | FOLFOX regimen + cetuximab (400 mg/m$^2$ IV loading dose, then cetuximab 250 mg/m$^2$ IV weekly thereafter OR cetuximab 500 mg/m$^2$ IV every 2 weeks) IV before FOLFOX<br>OR<br>FOLFOX regimen + panitumumab 6 mg/kg IV day 1 before FOLFOX<br>Repeat cycle every 2 weeks | FOLFOX: sensory neuropathy, neutropenia<br>Cetuximab: papulopustular and follicular rash, asthenia, constipation, diarrhea, allergic reactions, hypomagnesemia<br>Panitumumab: rash, diarrhea, hypomagnesemia | Only *RAS* wild-type tumor |
| FOLFIRI + cetuximab or panitumumab | FOLFIRI + cetuximab (400 mg/m$^2$ IV loading dose, then cetuximab 250 mg/m$^2$ IV weekly thereafter OR cetuximab 500 mg/m$^2$ IV every 2 weeks) IV before FOLFIRI<br>OR<br>FOLFIRI + panitumumab 6 mg/kg IV day 1 before FOLFIRI<br>Repeat cycle every 2 weeks | FOLFIRI: diarrhea, mucositis, neutropenia<br>Cetuximab: papulopustular and follicular rash, asthenia, constipation, diarrhea, allergic reactions, hypomagnesemia<br>Panitumumab: rash, diarrhea, hypomagnesemia | Only *RAS* wild-type tumor; preferred for patients with preexisting neuropathy or those in which neuropathy may be debilitating to their line of work (eg, musician) |

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| **Patients NOT Appropriate for Intensive Therapy with *RAS* Mutations** | | | |
| Infusional fluorouracil + leucovorin ± bevacizumab | Fluorouracil 400 mg/m$^2$ IV bolus, after leucovorin on day 1, then 1200 mg/m$^2$/day × 2 days CIV (total 2400 mg/m$^2$ over 46–48 hours)<br>Repeat cycle every 2 weeks<br>± Bevacizumab 5 mg/kg IV day 1 prior to fluorouracil and leucovorin<br>Repeat cycle every 2 weeks | Infusional fluorouracil/leucovorin: neutropenia, diarrhea<br>Bevacizumab: hypertension, bleeding, proteinuria | Infusional fluorouracil/leucovorin regimen preferred to bolus fluorouracil regimen |
| Capecitabine ± bevacizumab | Capecitabine 850–1250 mg/m$^2$ orally twice a day, days 1–14<br>± Bevacizumab 7.5 mg/kg IV day 1<br>Repeat cycle every 3 weeks | Capecitabine: hand–foot syndrome, diarrhea, hyperbilirubinemia<br>Bevacizumab: hypertension, thrombosis, proteinuria | |
| **Patients NOT Appropriate for Intensive Therapy with *RAS* or *BRAF* Wild-Type and Left-Sided Tumors** | | | |
| Cetuximab[c] | Cetuximab 400 mg/m$^2$ IV loading dose, then cetuximab 250 mg/m$^2$ IV weekly thereafter<br>OR<br>Cetuximab 500 mg/m$^2$ IV every 2 weeks | Papulopustular and follicular rash, asthenia, constipation, diarrhea, allergic reactions, hypomagnesemia | Only *RAS* wild-type tumor |
| Panitumumab[c] | 6 mg/kg IV over 60 minutes every 2 weeks | Rash, hypomagnesemia, rare allergic reactions | Only *RAS* wild-type tumor |
| **Patients NOT Appropriate for Intensive Therapy with dMMR or MSI-H** | | | |
| Nivolumab | 3 mg/kg IV every 2 weeks or 240 mg IV every 2 weeks[d] | Immune-mediated side effects (most common: skin, liver, kidney, gastrointestinal tract, lung, and endocrine systems) | Only in dMMR or MSI-H tumors. Patients should be closely monitored for side effects and report any side effects immediately as interruption of treatment or initiation of corticosteroids may be needed |
| Pembrolizumab | 2 mg/kg IV every 2 weeks or 200 mg IV every 3 weeks[d] | Immune-mediated side effects (most common: skin, liver, kidney, | Only in dMMR or MSI-H tumors. Patients should be closely monitored for side effects and report any side effects immediately as interruption of treatment or initiation of corticosteroids may be |

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| | | gastrointestinal tract, lung, and endocrine systems) | needed |
| Nivolumab + ipilimumab[c] | Nivolumab 3 mg/kg IV over 30 minutes and ipilimumab 1 mg/kg IV over 30 minutes every 3 weeks × 4 doses, then nivolumab 3 mg/kg IV or nivolumab 240 mg IV every 2 weeks[d] | Immune-mediated side effects (most common: skin, liver, kidney, gastrointestinal tract, lung, and endocrine systems) | Only in dMMR or MSI-H tumors. Patients should be closely monitored for side effects and report any side effects immediately as interruption of treatment or initiation of corticosteroids may be needed |

[a]National Comprehensive Cancer Network (NCCN) Guideline recommendations for initial therapy. All recommendations are Category 2A unless otherwise noted. Category 2A: based upon lower-evidence, there is uniform NCCN consensus that the intervention is appropriate.

[b]Original dosing was 1600 mg/m$^2$/day but it is recommended that US patients use this dose as they don't tolerate fluorouracil as well.

[c]NCCN Category 2B: based upon lower-evidence, there is NCCN consensus that the intervention is appropriate.

[d]Flat dosing is preferred.

### Unresectable MCRC

- Systemic chemotherapy palliates symptoms and improves survival in patients with unresectable disease. RT may control localized symptoms. Most MCRCs are incurable; however, randomized trials confirm that chemotherapy prolongs life and improves quality of life.
- Consider goals of therapy, history of prior chemotherapy, tumor *RAS* and MMR/MSI mutation status, performance status/comorbidities, and risk of drug-related toxicities to determine a management strategy. Regimens are the same for metastatic cancer of the colon and rectum.
- Accepted initial chemotherapy regimens incorporate a fluoropyrimidine. Addition of **irinotecan** or oxaliplatin significantly improves response rates, progression-free survival, and median survival. Addition of the targeted anti-angiogenesis agent **bevacizumab** further improves response rate and survival (see **Table 61-2**).
- **Capecitabine** monotherapy is suitable for first-line therapy in patients not likely to tolerate IV chemotherapy. Available for oral administration, it is converted to fluorouracil and is a suitable replacement for infusional fluorouracil in combination with oxaliplatin (CapeOx).
- Bevacizumab is a humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF). Addition of bevacizumab to fluorouracil-based regimens modestly increases PFS and OS as compared to chemotherapy alone.

  ✔ Hypertension is common with bevacizumab and easily managed with oral antihypertensive agents. Other safety concerns include bleeding, thrombocytopenia, and proteinuria. GI perforation is a rare but potentially fatal complication necessitating prompt evaluation of abdominal pain associated with vomiting or constipation. Bevacizumab can interfere with wound healing; schedule surgery at least 6 weeks after the last dose of bevacizumab and wait at least 6–8 weeks after surgery to restart.
- **Cetuximab** and **panitumumab** are EGFR inhibitors used in patients with wild-type *RAS* and wild-type *BRAF* tumors in combination with FOLFOX or FOLFIRI or administered alone (**Table 61-2**). Patients with left-sided primary tumors have improved overall survival when treated with EGFR inhibitors while those with right-sided tumors (cecum to hepatic flexure) do not. Severe infusion reactions, including anaphylaxis, can occur with cetuximab (3%) and panitumumab (1%). Skin toxicity is also commonly seen and is not part of the infusion reaction. The presence of papulopustular skin rash has been shown to correlate with response and survival and most commonly occurs within 2 to 4 weeks of therapy initiation.

- Patients may receive consecutive regimens; the sequence of drugs appears less important than exposure to all active agents in the course of chemotherapy treatments.

## Metastatic Disease: Second-Line and Subsequent Therapy

- The selection of second-line chemotherapy is primarily based on the type of and response to prior therapy received, site and extent of disease, and patient factors and treatment preferences. The optimal sequence of regimens has not been established (**Table 61-3**).
- Patients with wild-type *RAS* and wild-type *BRAF* tumors who experience progression on therapies that do not contain an EGFR inhibitor may benefit from the combination of cetuximab or panitumumab and irinotecan or FOLFIRI.
- Patients with *BRAF V600E* mutations may benefit from a regimen containing irinotecan and cetuximab with or without **vemurafenib** (a second-generation, select BRAF inhibitor) or a second regimen containing **dabrafenib** (a BRAF inhibitor), **trametinib** (a MEK inhibitor), and panitumumab (an EGFR inhibitor).
- Angiogenesis inhibitors including VEGF inhibitors bevacizumab, **ramucircumab**, and **ziv-aflibercept** and the oral multikinase inhibitor **regorafenib** may be used in patients with progressive disease.
- *HER2*, a member of the same kinase family as EGFR, is rarely overexpressed in CRC; however, it is more common in those with *HER2RAS* and *BRAF* wild-type tumors. *HER2* inhibitor therapy can be an option for those with *HER2* overexpression when other options have failed.
- **Pembrolizumab**, a humanized, IgG4 monoclonal antibody that binds to PD-L1 with high affinity, is effective in MCRC patients with dMMR who have progressed through 2–4 other regimens. **Nivolumab**, another humanized IgG4 monoclonal antibody PD-1 inhibitor, has also been evaluated with or without **ipilimumab** in patients with MCRC who have dMMR/MSI-H tumors.

TABLE 61-3

**Second-line and Salvage Chemotherapy Regimens for Metastatic Colorectal Cancer**[a]

| Disease Progression with First-Line Regimen | Comments |
|---|---|
| **First-Line Therapy: Oxaliplatin-Based Regimen +/- Bevacizumab (ie, FOLFOX, CapeOX)** | |
| Second-line options | |
| 1. FOLFIRI or irinotecan | Use with caution in patients with elevated bilirubin |
| 2. FOLFIRI + bevacizumab or ziv-afilbercept or ramucirumab | Use with caution in patients with elevated bilirubin; bevacizumab is preferred antiangiogenic agent based on toxicity and cost |
| 3. Irinotecan + bevacizumab or ziv-afilbercept or ramucirumab | Use with caution in patients with elevated bilirubin; bevacizumab is preferred antiangiogenic agent based on toxicity and cost |
| 4. FOLFIRI + cetuximab or panitumumab | Only if *RAS* wild-type and *BRAF* wild-type; if neither previously given; use with caution in patients with elevated bilirubin |
| 5. Irinotecan ± cetuximab or panitumumab | Only if *RAS* wild-type and *BRAF* wild-type; if neither previously given; use with caution in patients with elevated bilirubin |
| 6. Irinotecan ± (cetuximab or panitumumab) + vemurafenib | Only if *RAS* wild-type and *BRAF V600E* mutation positive; use with caution in patients with elevated bilirubin |

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| 7. Dabrafenib + trametinib + (cetuximab or panitumumab) | Only if *BRAF V600E* mutation positive |
| 8. Encorafenib + binimetinib + (cetuximab or panitumumab) | Only if *BRAF V600E* mutation positive |
| 9. Nivolumab ± ipilimumab | Only if dMMR/MSI-H |
| 10. Pembrolizumab | Only if dMMR/MSI-H |
| 11. Trastuzumab + (pertuzumab or lapatinib) | Only if *HER2*-amplified and *RAS* wild-type |
| **First-Line Therapy: Irinotecan-Based Regimen +/- Bevacizumab (ie, FOLFIRI)** | |
| Second-line options | |
| 1. FOLFOX or CapeOx ± bevacizumab | Bevacizumab FDA-approved to continue with second-line options |
| 2. FOLFOX + cetuximab or panitumumab | Only if *RAS* wild-type and *BRAF* wild-type |
| 3. Irinotecan + cetuximab or panitumumab | Only if *RAS* wild-type and *BRAF* wild-type; if neither previously given; use with caution in patients with elevated bilirubin |
| 4. Irinotecan + (cetuximab or panitumumab) + vemurafenib | Only if *RAS* wild-type and *BRAF V600E* mutation positive; use with caution in patients with elevated bilirubin |
| 5. Dabrafenib + trametinib + (cetuximab or panitumumab) | Only if *BRAF V600E* mutation positive |
| 6. Encorafenib + binimetinib + (cetuximab or panitumumab) | Only if *BRAF V600E* mutation positive |
| 7. Nivolumab ± ipilimumab | Only if dMMR/MSI-H |
| 8. Pembrolizumab | Only if dMMR/MSI-H |
| 9. Trastuzumab + (pertuzumab or lapatinib) | Only if *HER2*-amplified and *RAS* wild-type |
| **First-Line Therapy: Fluorouracil-Based Regimen +/- Bevacizumab (ie, Fluorouracil/Leucovorin, Capecitabine)** | |
| Second-line options | |
| 1. FOLFOX or CapeOx ± bevacizumab | |
| 2. FOLFIRI or irinotecan ± bevacizumab or ziv-afilbercept or ramucirumab | Bevacizumab has least toxicity and lower cost of antiangiogenic agents |
| 3. Irinotecan + oxaliplatin (IROX) ± bevacizumab | Use with caution in patients with elevated bilirubin |
| 4. Nivolumab ± ipilimumab | Only if dMMR/MSI-H |
| 5. Pembrolizumab | Only if dMMR/MSI-H |

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|---|---|
| 6. Trastuzumab + (pertuzumab or lapatinib) | Only if *HER2*-amplified and *RAS* wild-type |
| **Therapy After Second Progression or Third Progression** | |
| 1. Regorafenib | Used after progressed through all available regimens |
| 2. Irinotecan ± cetuximab or panitumumab | Only if *RAS* wild-type and neither previously given; use with caution in patients with elevated bilirubin |
| 3. Trifluridine/Tipiracil | Used after progressed through all available regimens |
| 4. Nivolumab ± ipilimumab | Only if dMMR/MSI-H and not previously given |
| 5. Pembrolizumab | Only if dMMR/MSI-H and not previously given |
| 6. Trastuzumab + (pertuzumab or lapatinib) | Only if *HER2*-amplified and *RAS* wild-type |
| 7. Clinical trial | If available and only if patient eligible |
| 8. Best supportive care | Appropriate for patients who do not want to pursue treatment or quality of life is expected to decrease |

[a]National Comprehensive Cancer Network (NCCN) Guideline recommendations for initial therapy. All recommendations are Category 2A unless otherwise noted. Category 2A: based upon lower-evidence, there is uniform NCCN consensus that the intervention is appropriate.

CapeOx, capecitabine plus oxaliplatin; dMMR, DNA mismatch repair deficiency; FOLFIRI, fluorouracil plus leucovorin plus irinotecan; FOLFOX, fluorouracil plus leucovorin plus oxaliplatin; MSI-H, high microsatellite instability.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Goals of monitoring are to evaluate benefit of treatment and detect recurrence.
- Patients who undergo curative surgical resection, with or without adjuvant therapy, require routine follow-up. Consult practice guidelines for specifics.
- Evaluate patients for anticipated side effects such as loose stools or diarrhea, nausea or vomiting, mouth sores, fatigue, and fever.
- Patients should be closely monitored for side effects that require prompt intervention, such as irinotecan-induced diarrhea, bevacizumab-induced GI perforation, hypertension and proteinuria, oxaliplatin-induced neuropathy, and cetuximab- and panitumumab-induced skin rash.
- Less than one-half of patients develop symptoms of recurrence, such as pain syndromes, changes in bowel habits, rectal or vaginal bleeding, pelvic masses, anorexia, and weight loss. Recurrences in asymptomatic patients can be detected because of increased serum CEA levels.
- Monitor quality-of-life indices, especially in patients with metastatic disease.

*See Chapter 147, Colorectal Cancer, authored by Lisa M. Holle, Jessica M. Clement, and Lisa E. Davis, for a more detailed discussion of this topic.*