Targeted, Evidence-Based Colorectal Cancer Therapies: Shifting the Patient Outcome

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Benson is active on numerous professional committees. He has served on several committees for the American Society of Clinical Oncology (ASCO) and is currently a member of the Task Force on Quality of Cancer Care and the Program and Education committees (chair of the Colorectal/Liver tract) and is cochair of both ASCO’s Colorectal Cancer Guidelines Subcommittee and the Stage II colon cancer guidelines panel. He also is the chair of the Eastern Cooperative Oncology Group Gastrointestinal and Data Monitoring committees. In addition, Benson is a member of several medical societies and serves as immediate past president of the Illinois Medical Oncology Society and as a trustee for the Association of Community Cancer Centers (ACCC) and is a member of the Board of Directors of the National Comprehensive Cancer Network (NCCN).

His research is primarily in the areas of gastrointestinal cancer clinical trials, cancer clinical trials, biologic therapies, phase I cancer clinical trials, and cancer guideline development. He has authored or coauthored numerous reports, reviews, and book chapters focusing on these topics. His research in biologics, cancer therapy, and cancer prevention has been awarded funding from a variety of sources, including the National Institutes of Health. Benson has been honored with several awards, including the Eastern Cooperative Oncology Group’s Young Investigator Award.
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Kaa received a PhD in pharmacy administration and health economics from the University of South Carolina and a BS in pharmacy from the University of Washington.

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Recent advances in the management of oncologic care and the challenges arising pursuant to change have been particularly interesting in the area of colorectal cancer (CRC). Good interfaces among different facets of care (e.g., medical management, pharmacy management, care management, case management, patient advocacy) have become crucial. Discussion of this topic is timely, especially with the increased scrutiny health care is currently experiencing from employer groups, insurance companies, and Medicare and Medicaid agencies.

An understanding of cancer, and especially CRC, is a journey that travels many roads. Some of them navigate through gastrointestinal cancer clinical trials, cancer clinical trials, biologic therapy development, or treatment guidelines. In addition, this “traveler” needs to look at reports, reviews, and book chapters. A variety of sources support the work that leads to these tools, including the National Institutes of Health, and the numerous Cooperative Oncology Groups across the nation, individual researchers and investigators, and even the Center for Medicare & Medicaid Services. The result: we have a better understanding of CRC’s epidemiology, tumor behavior at the cellular level, and preferred therapies than ever before. More important, therapies are emerging (and being reflected in the constantly changing standard of care) that have improved patient care in measurable ways. Therapy-induced toxicities are less severe, and in many cases, patients can be treated with less intrusive or oral therapies.

Managed care’s complexities and challenges related to cancer therapy are extensive. Clinicians and administrators must examine quality of life for patients, value associated with new and often costly therapies, and budget issues. Increasingly, we rely on informatics, reporting, and data analysis to guide our decisions. With regard to cancer, we need focused analyses, benchmarking activities, and financial impact models that are different from many developed to deal with other acute or chronic disease. And cancer’s impact has necessitated unique clinical evaluations, formulary development, and contract efforts. Managed care pharmacists need to know about the specific therapeutic interventions, utilization management programs, management reporting tools, and health services research that their organization will use to make decisions that best benefit their members.

Three changes ensure that cancer treatment will be a more pressing issue. First, many newer therapies are being formulated as oral agents. This moves medication from the physician’s office or clinic to community or outpatient pharmacies in terms of patient access and payment. Second, many new agents are
“-static” (as opposed to “-cidal”), meaning that they must be taken chronically to work. Third, our population is aging, and more than half of the people who develop CRC are Medicare beneficiaries who may be covered by Part D.

This brief summary of what is needed to understand CRC can seem overwhelming to the general practitioner and managed care decision makers who face similar knowledge needs in other, and until now, more common, health fields. Fortunately, the authors whose work appears in this supplement have the expertise necessary to describe the issues and the ability to translate hard science into readable, accurate, timely articles. Those who complete this supplement will find that they are better prepared to address the changing health care landscape that surrounds CRC treatment.

DISCLOSURES
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ABSTRACT

BACKGROUND: Every 3.5 minutes, someone is diagnosed with colorectal cancer (CRC); every 9 minutes, someone dies from CRC; and every 5 seconds, someone who should be screened for CRC is not. The 5-year mortality for people diagnosed with CRC is approximately 40%; however, survival improves substantially if the cancer is diagnosed while still localized.

OBJECTIVE: To track and review the rapid progress researchers have made in CRC.

SUMMARY: Among patients who have CRC, approximately 50% will eventually develop liver metastases. The oncology field’s significant advances in the last few years, especially in CRC, challenge clinicians and patients. Multiple facets of care intersect in CRC: medical management, pharmacy management, symptom management, case management, and patient advocacy. CRC develops over many years as environmental and genetic factors interact. The American Cancer Society recommends screening all men and women older than 50 years and those at high risk at an earlier age. In the past, patients presenting with the same stage of CRC were considered similar. The staging criteria of the American Joint Committee on Cancer recognizes that subsets of patients with varying survival statistics can be identified and that each patient requires a strategic approach. The U.S. Food and Drug Administration approval of irinotecan in 1996 and oxaliplatin in 2002 changed the landscape, and ultimately, the oral agent capecitabine and the biologics bevacizumab and cetuximab also significantly expanded treatment options.

CONCLUSION: Clinicians must consider all available treatment options and regimen sequences across multiple lines of therapy, creating an early plan for each patient to extend survival while minimizing side effects.

KEYWORDS: Bevacizumab, Capecitabine, Cetuximab, Colorectal cancer, FOLFOX, Irinotecan, Oxaliplatin, Panitumumab

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Colorectal Cancer Epidemiology

Every 7 seconds, someone turns 50 years old; every 3.5 minutes, someone is diagnosed with CRC; every 9 minutes, someone dies from CRC; and every 5 seconds, someone who should be screened for CRC is not. The 5-year mortality for people diagnosed with CRC is approximately 40%; however, survival improves substantially if the cancer is diagnosed while it is still localized. In a typical general practice with 500 patients older than 50 years, one would expect 100 to 250 of these patients to have colorectal adenomas. Ten to thirty of these patients would be expected to have CRC, and because only one third are apt to be screened, two thirds of these patients may die unnecessarily. Unfortunately, 20% of CRC patients who do receive screening may be diagnosed in the later, less-treatable stages.

The good news is that CRC’s incidence rate declined by 2.9% annually from 1998 to 2001. Regardless, colorectal cancer remains the third most common cancer in men and women in the United States. The decline in incidence may have been due, in part, to increased screening and polyp removal. The National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) Program monitors the incidence of all cancers throughout the United States. For both men and women, the incidence of CRC begins to rise around the age of 40 years. Incidence sharply increases at age 50 years; 92% of CRCs are diagnosed in persons aged 50 years or older. People in their 80s clearly continue to be at risk for CRC, with 12.5% of cases diagnosed after age 85.

Because age is a significant risk factor and the American population is aging, the population of individuals at risk for CRC is larger than it has ever been.
CRC is very common worldwide, with 850,000 people developing it annually and 500,000 dying of the disease.6,7 Its prevalence and preventable nature makes CRC a primary focus in the oncology community. In fact, estimates indicate that gastrointestinal cancers represent about 20% of all cancers. The broad diversity in the types of patients and stages at which the disease is diagnosed creates multidisciplinary challenges.

Among patients who have CRC, a majority will eventually develop liver metastases. In 30% to 40% of CRC patients, metastases are confined to the liver when they are initially found. One quarter to one third of patients who are able to undergo resection of liver metastases will live 5 years or longer; median survival after resection is between 24 and 40 months. This high rate of liver metastases has transformed treatment and evaluation in an effort to improve cure rates.3,8 More recent data indicate that survival rates may be increasing.3,8

The risk factors for CRC for people who live in the United States are presented in Table 1. CRC does not discriminate by gender or ethnicity in terms of incidence or mortality. Socioeconomic groups in the lower income ranges tend to present with more advanced disease. Men tend to develop CRC slightly more often than women.2 The disease affects all ethnic groups, and epidemiologic studies confirm that environmental exposure is probably a factor. For example, people who immigrated to the United States from Japan—where CRC was once a low-incidence disease—eventually developed CRC at a rate similar to native-born Americans. Today, Japan’s incidence of CRC is rising dramatically, probably due to Western influence, particularly in diet; dietary intake of milk, meat, eggs, and fat/oil increased remarkably in Japan from 1950 to 1970, and it remains at this elevated level today.9 Globally, some differences in incidence remain related to location and low socioeconomic status. Japan’s experience supports what we know: diet is a leading risk factor for CRC.

CRC is considered a completely preventable disease by most experts, and the fact that many of its risk factors are related to lifestyle reflect that belief. High-fat diets with few fruits and vegetables, inactivity, obesity, smoking, and alcohol use increase risk. Interest in chemoprevention is high, and trials suggest that nonsteroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen) and cyclooxygenase-2 (COX-2) inhibitors (such as rofecoxib or celecoxib) may reduce the risk of CRC. The CRC-related mortality has been reduced 40% to 50% in individuals who regularly take aspirin and other NSAIDs. Additionally, COX-2 is elevated in 85% to 95% of CRCs; overexpression has been shown to decrease cancer cell death.10,11 One study of a COX-2 inhibitor (celecoxib) showed a significant reduction in polyps.12,14

Approximately 70% of CRCs are nonhereditary, or sporadic, and about 20% are familial. Two key hereditary syndromes are familial adenomatous polyposis (FAP) and hereditary nonpolyposis colon cancer (HNPPC). The FAP syndrome develops from inherited mutations of the adenomatous polyposis coli (APC) gene, and accounts for approximately 1% to 2% of all CRC cases. Patients with FAP develop hundreds to thousands of polyps before age 30, and inevitably develop CRC. Usually, CRC develops at an early age (average, 39 years) in FAP patients, but it can be prevented by surgically removing the colon.15

Lynch syndrome, or HNPPC, is caused by inherited mutation in any 1 of 5 mismatch repair (MMR) genes, and accounts for 3% to 5% of all CRC cases. The term nonpolyposis does not mean that the cancer does not emanate from polyps; it is used to distinguish HNPPC from FAP. Polyps do not develop earlier in people with HNPPC, but once they do, their tendency to become malignant more rapidly leads to a 70% to 80% lifetime risk of CRC. In these patients, CRC occurs at early age (average 44 years). Some patients with HNPPC also elect to have a complete colectomy because of their increased risk of rapid development of colon cancer. Experts stress the need for detailed family history to identify individuals who are at risk to provide appropriate screening, genetic counseling, and treatment. It has been recommended that people who have a first-degree relative who has had CRC should be screened annually beginning at age 40, rather than at age 50. Family members of patients who developed CRC very early (i.e., before age 50) should be screened 10 years before the age at which the relative developed CRC. For example, if a patient’s brother, or other first-degree relative, developed CRC at age 45, the patient should begin screening at age 35.16-18

### The Biology

Approximately 70% to 90% of CRCs arise from adenomatous polyps. Between 15% and 30% of people in the United States eventually develop polyps—about 30% of all polyps are hyperplastic with no malignant potential. Others are adenomatous and

![Table 1: Risk Factors for Colorectal Cancer (CRC)](https://example.com/table1.png)

<table>
<thead>
<tr>
<th>Factor</th>
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<tbody>
<tr>
<td>Age older than 50 years</td>
</tr>
<tr>
<td>Previous CRC</td>
</tr>
<tr>
<td>Polyps</td>
</tr>
<tr>
<td>Family history of CRC or adenomatous polyps</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>– Ulcerative colitis</td>
</tr>
<tr>
<td>– Crohn’s disease</td>
</tr>
<tr>
<td>Preventable risk factors</td>
</tr>
<tr>
<td>– High-fat diet</td>
</tr>
<tr>
<td>– Diet low in fruits and vegetables</td>
</tr>
<tr>
<td>– Physical inactivity</td>
</tr>
<tr>
<td>– Obesity</td>
</tr>
<tr>
<td>– Smoking</td>
</tr>
<tr>
<td>– Alcohol</td>
</tr>
<tr>
<td>Possible chemoprevention</td>
</tr>
<tr>
<td>– NSAIDs, COX-2 inhibitors</td>
</tr>
</tbody>
</table>

COX-2 = cyclooxygenase isoenzyme 2; NSAID = nonsteroidal anti-inflammatory drugs.
are considered premalignant. Polyps larger than 2 cm in diameter have a 50% chance of becoming malignant. Polyp removal, although not perfect, dramatically reduces the incidence of colorectal cancer. Previous CRC increases risk for a new primary tumor at least 4-fold; therefore, regular screening with colonoscopy becomes a lifelong requirement for these patients. In addition, people with inflammatory bowel disease, particularly ulcerative colitis and Crohn’s disease, must be screened very carefully because of their substantial risk of developing cancer.

Our understanding of the molecular biology of colon cancer has grown exponentially in recent years. Colorectal cancer develops over many years as environmental and genetic factors interact. Environmentally, a high-fat diet plays a role in the development of CRC, especially in the descending and sigmoid colon. Fat makes up 40% to 50% of total caloric intake in Western countries. Animals fed high-fat diets develop more carcinogen-induced colon cancers than do animals on low-fat diets.

Dietary fats are converted into potentially carcinogenic substances and enhance cholesterol and bile acid synthesis by the liver. Bacterial flora convert these compounds to secondary bile acids, cholesterol metabolites, and other potentially toxic metabolites. Bile acids may activate protein kinase C—an enzyme involved in the transfer of cell signals that, when activated, induce excess cellular production.

Colorectal cancer arises as genetic alterations that cause abnormal cellular proliferation, resulting in progression from normal colonic mucosa to adenomas or adenomatous polyps to adenocarcinoma. This progression can be induced by a series of inherited or noninherited mutations involving oncogenes and tumor suppressor genes. Inherited APC and MMR mutations are responsible for the 2 most common types of hereditary CRC. These genes are also involved in noninherited mutations, along with Kirsten-ras (K-ras), p53, and other genes. Noninherited mutations of the APC gene are also present in 60% to 80% of sporadic CRC and adenomas.

• hMLH1 is the MMR gene most commonly mutated in sporadic CRCs, especially those occurring in the right or transverse colon.
• K-ras is an important proto-oncogene involved in the regulation of cell proliferation. K-ras mutations are present in about 40% of CRCs.
• p53 is a tumor suppressor gene normally involved in preventing cells with damaged DNA from progressing through the cell cycle. This gene also inhibits angiogenesis, possibly by decreasing expression of vascular endothelial growth factor (VEGF). Loss of p53 is present in approximately 75% of CRC and is involved in the conversion of adenoma to adenocarcinoma.

The sequence of molecular events is not a linear, but rather a collection of events that occurs over time. Using large tumor banks (repositories for tissue specimens), researchers may someday link colon cancer clinical trial efficacy data to develop both prognostic and predicted strategies based on the tumor’s molecular biology. This information will allow clinicians to fine-tune the approach for each individual patient.

### Diagnosis and Screening

Symptoms of CRC can be nonspecific or quite fulminating. Patients may interpret occult blood in stool as hemorrhoids and fail to pursue treatment. Then again, blatant hematochezia (bloody stool) or melena (dark tarry feces containing blood) may cause patients to seek immediate treatment. Anemia may be identified serendipitously or during routine physical examination, and subsequent evaluation may find otherwise asymptomatic colon cancer. Change in bowel habits is a common symptom, particularly among individuals whose tumors grow in the sigmoid colon or rectum.

The American Cancer Society recommends screening all men and women older than 50 and those at high risk at an earlier age. Unfortunately, many Americans fail to schedule screenings. Currently, colonoscopy remains the gold standard for screening and diagnosis. Sigmoidoscopy can only evaluate the rectum and the left side of the colon, and this is a serious limitation. For example, people with HNPCC syndrome are much more likely to have a silent right-sided colon cancer. Flexible sigmoidoscopy may be done every 5 years but must be coupled with fecal occult blood testing annually. If an individual has a positive fecal occult blood test even with a negative sigmoidoscopy, that individual must be fully evaluated with the colonoscopy. Also, double contrast barium enema is occasionally used as a screening tool.

The standard approach to preventing CRC is to employ routine screening and remove colon polyps.

Staging has evolved over time, and we currently use the TNM system, an evaluation system based on 3 variables: primary tumor (T), regional nodes (N), and metastasis (M). Table 2 provides the newest CRC staging. In the past, patients presenting with the same stage of CRC were considered similar. The new staging criteria recognize that they are usually quite different. Within the confines of the staging system, subsets of patients with varying survival statistics can be found. Stage II colon cancer is now subdivided into stage IIA and stage IIB, and stage III into Stages IIIA, IIIB, and IIIC. Fewer than one quarter of patients present with early disease (Stage I) that is curable by surgical resection. Staging appropriately dramatically improves survival. In large part, the present discussion focuses on stage IV disease, which represents more than 20% of CRC patients at diagnosis.

Managed care pharmacists may be unfamiliar with cancer terminology in general, and treatment of CRC specifically. Table 3 defines some terms necessary to understand recent changes in its diagnosis and treatment. Surgery has always been the treatment of choice for CRC. Radiation generally is restricted to rectal cancers. Additionally, readers should keep in mind that until the mid-1990s, chemotherapy for CRC was limited to 5-fluorouracil (5-FU) plus radiation.
and oxaliplatin in 2002 changed the landscape, and ultimately, the biologics bevacizumab and cetuximab also significantly expanded treatment options. Oncology is also a field that uses many (and sometimes confusing) acronyms. These, too, are addressed in Table 3. Sometimes, clinicians, researchers, or institutions modify standard regimens, and they are then given a similar but new name (e.g., FOLFOX4, FOLFOX6).

The most common treatment for patients with localized CRC is surgery, which is frequently curative. Although adjuvant chemotherapy in stage II disease has been investigated, its use remains controversial, with overall survival ranging from approximately 75% to 80% with surgery alone. Surgery and adjuvant chemotherapy are common treatments for patients with stage III disease. Conversely, the overall survival among individuals with stage IIIC colon cancer, even after surgical resection, is as low as 15%. The differences in survival are striking. Combination chemotherapy is given for metastatic disease when possible. Chemotherapy with radiation is given before (favored) or after surgery in most patients with stage II or III rectal cancer. Thus, one strategy for all patients is inappropriate.25 Case 1 introduces these issues (see Sidebar 1).

Fortunately, guidance is available for clinicians. The NCCN has created treatment guidelines for almost every cancer and for the most common treatment-induced symptoms.26 All are available online at www.nccn.org. The colon cancer guidelines are currently under evaluation and are reviewed at least annually, but rapid changes in CRC have prompted NCCN to revise and update the guidelines more often. In the algorithm for a patient like the one described in Case 1 (see Sidebar 1) with proven metastatic adenocarcinoma, NCCN suggests separating patients into 3 groups: those with liver metastases, those with lung metastases, and those with more disseminated disease.

For patients presenting with liver metastases at the first diagnosis, clinicians can select one of several pathways. Treatment might begin with chemotherapy with a biologic, and depending on patient response, make a decision about whether to proceed with the primary tumor removal and liver resection. Alternatively, the oncologist might schedule surgery to remove the primary colon lesion and perhaps remove the liver lesion. Liver resection, if feasible, can also be scheduled for a later time. Another option is colectomy followed by neoadjuvant chemotherapy and then liver resection.

Patients unable to undergo curative resection must be evaluated for symptoms. Bleeding or obstruction may be an indication for surgery before chemotherapy. In relatively asymptomatic patients, proceeding with chemotherapy can shrink the primary tumor as well as metastatic disease. Oncologists generally find that among patients with hepatic metastases, approximately 70% are considered resectable at diagnosis. However, a sizable number of patients even with multiple lesions may be able to undergo successful surgery.

Numerous studies have examined surgical rates in patients with metastatic colon cancer who have had surgical resection, and the 5-year survival rate (the point at which oncologists consider a patient cured) ranges from 25% to nearly 60%, compared with patients with metastatic disease who have not had resection; their 5-year survivorship rate is between 5% and 10%.27-33

### Table 2

<table>
<thead>
<tr>
<th>Disease development</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staging</td>
<td>T1 N0 M0</td>
<td>A: T3 N0 M0</td>
<td>A: T1-2 N1 M0</td>
<td>Any T Any N M1</td>
</tr>
<tr>
<td></td>
<td>T2 N0 M0</td>
<td>B: T4 N0 M0</td>
<td>B: T3-4 N1 M0</td>
<td>Any N M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: Any T N2 M0</td>
<td>Any N M1</td>
</tr>
<tr>
<td>Definition</td>
<td>Invades submucosa (T1)/muscular propria (T2)</td>
<td>Invades subserosa, nonperitonealized pericolic/perirectal tissues (T3)</td>
<td>Involves 1-3 (N1) or more (N2) lymph nodes</td>
<td>Involves distant metastases</td>
</tr>
<tr>
<td>Usual treatment</td>
<td>Surgery</td>
<td>Surgery &amp; chemotherapy</td>
<td>Surgery &amp; chemotherapy</td>
<td>Chemotherapy &amp; surgery</td>
</tr>
</tbody>
</table>

Epidemiology, Disease Progression, and Economic Burden of Colorectal Cancer

### TABLE 3: Colorectal Cancer Terms and Acronyms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant chemotherapy</td>
<td>Chemotherapy treatment that is given after complete surgical resection of cancer. Its aim is to treat presumed residual micrometastatic disease.</td>
</tr>
<tr>
<td>CEA</td>
<td>Carcinoembryonic antigen, a serum marker often elevated in people with some adenocarcinomas, in particular colon cancer. It may also be present in the serum of patients with pancreas, breast, ovary, or lung cancer. CEA is normally produced during the development of a fetus. Production stops before birth, and it usually is minimally present in the blood of healthy adults.</td>
</tr>
<tr>
<td>CapIri</td>
<td>A regimen similar to FOLFIRI (see below)</td>
</tr>
<tr>
<td>CapOx</td>
<td>A regimen similar to FOLFOX (see below) that substitutes oral capecitabine for intravenous fluorouracil</td>
</tr>
<tr>
<td>Downstage</td>
<td>Employment of chemotherapy or chemoradiation to reduce tumor burden and thus reduce the clinical stage of the disease</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>A chemotherapy regimen for treatment of advanced colorectal cancer or adjuvant treatment, consisting of concurrent treatment with fluorouracil, leucovorin (folinic acid), and oxaliplatin. Patients typically receive a treatment every 2 weeks, and leucovorin and oxaliplatin are administered as an infusion lasting 2 hours, followed by fluorouracil, which is administered in 2 different ways: a bolus injection and a continuous infusion lasting 46 hours.</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>A chemotherapy regimen for treatment of advanced colorectal cancer, consisting of concurrent treatment with irinotecan, leucovorin (folinic acid), and fluorouracil. A standard regimen would include irinotecan as a 90-minute infusion concurrently with a fluorouracil bolus, then fluorouracil intravenous infusion over 46 hours. This cycle is typically repeated every 2 weeks.</td>
</tr>
<tr>
<td>IFL</td>
<td>A chemotherapy regimen for treatment of colorectal cancer that employs bolus fluorouracil and leucovorin with irinotecan—IFL is no longer recommended as a treatment regimen.</td>
</tr>
<tr>
<td>IROX</td>
<td>A chemotherapy regimen using irinotecan and oxaliplatin without fluorouracil</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>A chemotherapy treatment that is given before surgery</td>
</tr>
</tbody>
</table>

Prognostic factors, however, may be evolving with the introduction of modern chemotherapy approaches.5

#### Approaches for Liver Metastases

Hepatic artery infusion (HAI) is the infusion of chemotherapy into the hepatic artery via a surgically implanted pump. Chemotherapy drugs can be injected periodically into the chamber of the pump, which then employs a gas-driven bellows to send chemotherapy by a hepatic artery catheter directly into the liver. Fluorodeoxyuridine (FUDR) has been the chemotherapy of choice for many years for HAI; compared with other agents, FUDR has the highest rate of extraction by the liver. Trials have compared HAI to systemic therapy with fluorouracil.34-40 They have certain limitations and do not confirm a definitive survival benefit, but prior to the introduction of intravenous combination therapy, HAI produced the highest response rate seen in colon cancer: 50% to 60%. Since response rates with FOLFOX and FOLFIRI are similar to HAI, there may be a more limited role for HAI-delivered therapy.

Hepatic artery infusion has been tested for patients whose liver metastases have been resected.34-40 These trials are also imperfect; however, they show without question that HAI recipients tend to experience less hepatic recurrence than those who did not.
Experience with radiofrequency ablation (RFA, the use of electrodes to heat and destroy abnormal tissue) in patients with hepatic metastasis from CRC is increasing. Open surgery, percutaneous RFA, and laparoscopic RFA have been studied. Findings cannot confirm that RFA is curative—recurrence rates range from very low to almost 50% depending on the underlying presentation and number of lesions. \(^{41-48}\) If cure is the goal, surgical resection remains the gold standard, but in patients who are not good surgical candidates, RFA may be an option. Currently, many surgical patients have a combination of surgical resection with concurrent interoperative RFA for lesions that cannot be resected; the cure rate is unknown.

Adam et al. evaluated the long-term survival of patients who initially had inoperable colorectal liver metastases that subsequently responded to systemic chemotherapy and eventually allowed surgical resection.\(^8\) They used prognostic factors of outcome to create a model predicting survival in a preoperative setting. In a consecutive series of 1,439 patients with colorectal liver metastases from 1988 to 1999 at one hospital, 335 (23%) received initial resection, and 1,104 (77%) initially unresectable patients were treated with oxaliplatin-based or irinotecan-based chemotherapy, although 12% of patients received fluorouracil and leucovorin alone. After a documented response to chemotherapy was observed, 138 (12.5%) of patients underwent secondary hepatic resection resulting in a 33% 5-year survival. An average of 10 courses of chemotherapy were administered preoperatively. The 5-year survival was 48% for the initial surgical resection group. Four preoperative risk factors (a rectal tumor, an elevated CA 19-9, tumor larger than 10 cm, and 3 or more metastatic sites) predicted poorer outcome from this strategy. Neoadjuvant therapy results are changing the way oncologists think about patients with metastatic disease, introducing the concept of surgical resection for patients with previously unresectable disease. Survival expectancy at 5 years for patients with risk factors was also reported: 1 risk factor, 23% to 41%; 2 risk factors, 14%; and 3 or 4 risk factors, 0% to 1%. Although chemotherapy can produce a complete response as measured by CAT scan, most patients will have residual tumor cells visible in pathology specimen; therefore, we can not say at this time that neoadjuvant chemotherapy alone is curative.

With FOLFOX, the maximum reduction in tumor size is usually seen within 3 months. In addition, longer periods of chemotherapy administration can produce liver toxicities with non-alcoholic steatohepatitis, which can potentially increase surgical morbidity. Therefore, NCCN currently recommends administering approximately 3 months of chemotherapy, then surgery, and then additional chemotherapy after surgery. Clinical trials are currently exploring this approach. The strategy is identical for people with isolated lung metastases.\(^{26}\) Advanced metastatic disease is usually terminal. NCCN recommends that for patients who present with, for example, abdominal peritoneal disease, clinicians first rule out obstruction. Chemotherapy is an immediate option in nonobstructing disease, but other options (colon resection, colostomy, bypass, or stenting) must be considered if an obstruction is present. Cases 2 and 3 demonstrate some of these principles (see Sidebar 2).\(^{26}\)

In 2002, the FDA approved oxaliplatin, a third-generation platinum analog that induces DNA cross-links and results in apoptosis. Currently, it is approved for both the first- and second-line therapies of CRC. The biologics made their entry shortly thereafter. Bevacizumab is a humanized monoclonal antibody to VEGF, a key regulator of tumor angiogenesis. Approved in 2004, it is used in combination with fluorouracil regimens as first-line or second-line treatment for metastatic CRC. Cetuximab is a chimeric antibody to the epidermal growth factor receptor (EGFR) and was approved in 2004 for the treatment of second-line

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**Sidebar 2**

**Case 2**

A 56-year-old male presents with a nearly obstructing sigmoid cancer with extensive liver metastases. He undergoes sigmoid resection. Four weeks postoperatively, his performance status is 2 and his CEA is significantly elevated at 1,800 ng/mL. Options include capectabine, FOLFIRI, FOLFOX, IFI, infusional fluorouracil, fluorouracil/leucovorin, bevacizumab plus chemotherapy, and cetuximab plus chemotherapy.

This patient actually was treated with daily continuous venous infusion fluorouracil but required a dose reduction secondary to mucositis. Fortunately, he achieved a partial response and his performance status improved significantly. Although he is now asymptomatic, his liver metastases have progressed.

The key point in this case is that patients with bulky disease who are chemotherapy-naïve and are symptomatic pose clinical challenge. Some clinicians, concerned about the patient’s performance status, would opt for infusional fluorouracil or capectabine or fluorouracil or leucovorin. This would be an appropriate choice according to the NCCN guidelines. This may be the sole chance for treatment, however, and giving this individual the best opportunity for response may be critical. Although this patient responded to infusional fluorouracil, that is not always the case. Some oncologists might favor combination therapy up front even with an impaired performance status, hoping for rapid response and improved overall outcome.

**Case 3**

Two years ago, a 70-year-old male underwent a right hemicolectomy for a stage II colon cancer and did not receive adjuvant therapy. His CEA is now 100 ng/mL, and his chemistries are normal. Despite an excellent performance status, he has lung and liver metastases. In this case, FOLFOX or FOLFIRI with bevacizumab would be favored by most oncologists as first-line therapy.

Single-agent fluorouracil was the mainstay of treatment for CRC for decades. Advances in the treatment of CRC were galvanized by Saltz and colleagues’ publication,\(^{49}\) promulgating irinotecan as first-line therapy; concurrently, oncology’s philosophy about therapy also shifted. In 1996, the FDA approved irinotecan, a topoisomerase I inhibitor, as a second-line treatment for patients with metastatic CRC. Capecitabine, an oral fluoropyrimidine prodrug, was approved in 1998 for metastatic breast cancer. In 2002, the FDA approved an additional indication—metastatic CRC—for capecitabine. Capecitabine is converted to fluorouracil by a 3′-enzyme pathway including thymidine phosphorylase.
metastatic CRC in patients who over-express EGFR. Cetuximab in combination with irinotecan is indicated for patients who are refractory to irinotecan-based chemotherapy. As a single agent, cetuximab is indicated for patients who are intolerant to irinotecan-based chemotherapy.

Grothey and colleagues analyzed data from 7 phase 3 trials (N=3187) in advanced CRC to compare the proportion of patients receiving fluorouracil-leucovorin, irinotecan, and oxaliplatin administered over time with median overall survival (OS), using a weighted analysis. They reported median OS correlated significantly with the percentage of patients who received all 3 drugs (but no biologies) in the course of their disease. It did not correlate with the percentage of patients who received any second-line therapy. The use of combination therapies as first-line therapy was associated with an improvement in median survival of 3.5 months (95% confidence interval [CI], 1.27-5.73 months; P=0.0083). This represented a dramatic shift in survivorship from roughly 13% to nearly 22% and in median survivorship at 2 years. Their conclusion: the 3 active drugs should be available to all appropriate patients with advanced CRC to maximize OS. They also proposed that OS is not the most appropriate endpoint to assess the efficacy of a first-line treatment in CRC.

An updated report including 4 additional phase 3 trials (for a total of 11 studies, N=5,768) validated the initial analysis. It confirmed that the percentage of patients with advanced CRC receiving 3 drugs during the course of their disease were likely to have longer OS. Again, the researchers gathered data on exposure to fluorouracil-leucovorin, irinotecan, and oxaliplatin. They concluded that a strategy of making all active agents available to patients with advanced CRC appears to be more important than the use of an individual therapy, and that combination therapy should remain the standard of care for first-line treatment.

**The Treatment Continuum**

Clinicians now have more options for treating patients with CRC. This treatment continuum defines a strategic approach for each patient. It encourages consideration of all available treatment options and regimen sequences across multiple lines of therapy, creating an early plan for each patient to extend survival while minimizing side effects. Flexibility is crucial, too, so patients who experience oxaliplatin neurotoxicity, for example, can be shifted to a different but equally effective regimen. This replaces the “treat as you go” approach used historically. The treatment continuum concept is consistent with the current NCCN guidelines for metastatic CRC treatment and puts the guidelines in the context of patient benefits.

Safety and efficacy are emphasized as researchers have examined not only different drugs, but also different administration techniques. For example, in Europe, there is traditionally more emphasis on continuous infusion fluorouracil; this regimen is believed to be safe, more efficacious, and more conducive to combination therapy. This belief led to the development of infusion regimens, including FOLFOX and FOLFIRI. In the United States, researchers and clinicians emphasized bolus therapy. The evidence, however, now indicates continuous intravenous infusion (CIV) is clearly safer.

The Meta-analysis Group in Cancer conducted a meta-analysis of all randomized trials (N=1,219) that compared fluorouracil bolus with CIV, including toxicities, especially grades 3 to 4 anemia, thrombocytopenia, leukopenia, neutropenia, nausea/vomiting, diarrhea, mucositis, and hand-foot syndrome. They found that fluorouracil bolus was more likely to cause hematologic toxicity, mainly neutropenia (31% with bolus versus 4% with CIV, P<0.0001) but less likely to be associated with hand-foot syndrome (13% with bolus versus 34% with CIV, P<0.001).

The other nonhematologic toxicities did not differ significantly between groups. Independent prognostic factors were age, gender, and performance status for nonhematologic toxicities; they were performance status and treatment for hematologic toxicities and age, gender, and treatment for hand-foot syndrome.

Saltz et al. showed that irinotecan prolongs survival in CRC patients. They compared cohorts receiving either a combination of irinotecan and bolus fluorouracil and leucovorin (IFL) or bolus doses of fluorouracil and leucovorin as first-line therapy for metastatic CRC. A third group of patients received irinotecan alone. Endpoints were progression-free survival and overall survival. Patients were randomly assigned to receive:

- irinotecan (125 mg/m² IV), fluorouracil (500 mg/m² bolus), and leucovorin (20 mg/m² bolus) weekly for 4 weeks every 6 weeks (N=231); or
- fluorouracil (425 mg/m² bolus) and leucovorin (20 mg/m² bolus) daily for 5 consecutive days every 4 weeks (N=226); or
- irinotecan alone (125 mg/m² IV) weekly for 4 weeks every 6 weeks (N=226).

In an intention-to-treat analysis, treatment with irinotecan, fluorouracil, and leucovorin resulted in significantly longer progression-free survival (median, 7 months versus 4.3 months; P=0.004), a higher rate of confirmed response (39% versus 21%; P<0.001), and longer overall survival (median, 14.8 months versus 12.6 months; P=0.04) than irinotecan alone or fluorouracil and leucovorin. Results for irinotecan alone were similar to those for fluorouracil and leucovorin. On the basis of analysis of adverse events, adding irinotecan to the regimen of fluorouracil and leucovorin did not compromise the quality of life.

A second trial also examined the efficacy of irinotecan and fluorouracil to treat 387 previously untreated patients. They were randomly assigned to irinotecan plus infusion fluorouracil and leucovorin (N=199) or an infusion fluorouracil-leucovorin combination alone (N=188). Investigators could prescribe a once-weekly or every-2-weeks treatment cycle. The response rate was significantly higher in patients in the irinotecan group than in those in the no-irinotecan group (49% as opposed to 31%; P<0.001), as was time-to-progression (median 6.7 as opposed to 4.4 months; P<0.001). Overall survival was also
higher (median 17.4 as opposed to 14.1 months). Patients receiving irinotecan were more likely to develop some grade 3 and 4 toxic effects, but did so in a predictable manner. Adverse events were reversible, noncumulative, and manageable. The investigators suggested that the combination therapy be considered as a reference first-line treatment for metastatic CRC.

**Evolving First-Line Treatments**

Goldberg et al. looked at 3 different 2-drug combinations in patients with advanced metastatic CRC who were previously untreated. Patients were randomly assigned to receive
- irinotecan and bolus fluorouracil plus leucovorin (IFL, control combination), or
- oxaliplatin and infused fluorouracil plus leucovorin (FOLFOX), or
- irinotecan and oxaliplatin (IROX).

The investigators accrued 795 patients between May 1999 and April 2001. FOLFOX was associated with a median time-to-progression of 8.7 months, response rate of 45%, and median survival time of 19.5 months. These results were significantly superior to all endpoints observed for IFL (6.9 months, 31%, and 15 months, respectively) and for time-to-progression and response for IROX (6.5 months, 35%, and 17.4 months, respectively). The FOLFOX regimen’s adverse event profile was significantly better in terms of severe nausea, vomiting, diarrhea, febrile neutropenia, and dehydration. It was, however, associated with more sensory neuropathy and neutropenia. Thus, the investigators found the FOLFOX regimen active and comparatively safe. In addition to supporting FOLFOX as first-line treatment for metastatic CRC, the irinotecan/oxaliplatin regimen is an appropriate alternative for fluorouracil-intolerant individuals.

In Europe, the FOLFOX and FOLFIRI infusion schedules were both used. An Italian research group compared FOLFIRI with FOLFOX in previously untreated patients (N = 360) with advanced CRC. Patients were randomly assigned to receive, every 2 weeks, either
- arm A (N = 164) FOLFIRI: irinotecan 180 mg/m² on day 1 with leucovorin 100 mg/m² administered as a 2-hour infusion before fluorouracil 400 mg/m² administered as an intravenous bolus injection, and fluorouracil 600 mg/m² as a 22-hour infusion immediately after fluorouracil bolus injection on days 1 and 2 (LV5FU2) or
- arm B (N = 172) FOLFOX4: oxaliplatin 85 mg/m² on day 1 with the LV5FU2 regimen).

Overall response rates were 31% in arm A and 34% in arm B. Median time-to-progression, duration of response, and overall survival were similar in both arms. Patients in arm A reported more alopecia and gastrointestinal disturbance; those in arm B experienced more thrombocytopenia and neurosensory adverse effects. Serious toxicity was uncommon for both regimens. Both therapies are equally effective as first-line treatments, although their toxicity profiles differ.

Tournigand et al. randomized patients to FOLFOX6 or FOLFIRI and allowed crossover to the other regimen after disease progression. In arm A, 109 patients received FOLFIRI and 81 of these patients were treated with second-line FOLFOX upon progression. In arm B, 111 patients received FOLFOX and 69 of these patients were treated with second-line FOLFOX upon progression. Median survivals were similar in the arms: 21.5 months in arm A versus 20.6 months in arm B. Median second progression-free survival was 14.2 months in arm A versus 10.9 months in arm B. First-line response rates were similar, 54% and 56%, respectively. Grade 3/4 mucositis, nausea/vomiting, and grade 2 alopecia were more frequent with FOLFIRI, and grade 3/4 neutropenia and neurosensory toxicity were more frequent with FOLFOX6. This trial indicates that the sequence used is irrelevant; overall survival of about 21 months is expected with either approach. Either regimen is an appropriate platform on which to build other treatment approaches. The differences in toxicities may guide treatment choice.

**Enter Oral Agents**

Two randomized phase 3 trials compared oral capecitabine monotherapy with the Mayo regimen of intravenous bolus fluorouracil and leucovorin (daily for 5 days) as first-line therapy in patients with newly diagnosed metastatic CRC. Data obtained from each trial were pooled. Patients received either capecitabine 2,500 mg/m² daily (1,250 mg/m² twice daily) on days 1 to 14 every 21 days, or fluorouracil 450 mg/m² plus leucovorin 20 mg/m² IV daily on days 1 to 5 every 28 days. The primary endpoint was the overall objective tumor response rate (RR: complete response and partial response). Capecitabine treatment was associated with significantly higher RR than fluorouracil and leucovorin (25.7% versus 16.7%, respectively). However, no difference in overall survival (median of 12.9 months with each) between treatments was observed. Subgroup analysis indicated that the difference in response was observed irrespective of previous adjuvant therapy, site of metastasis, or age. A dose of capecitabine 2,500 mg/m² daily is higher than would be generally used in clinical practice in the United States, with most practitioners administering 2,000 mg/m². By observation, clinicians have determined that people in the United States do not tolerate capecitabine in the same doses that Europeans do. One theory is that the heavily fortified diet in the United States is folate-rich, accounting for increased fluoropyrimidine toxicity.

Studies of combinations of capecitabine identical to those using FOLFOX and FOLFIRI have been reported. Building on their previous work, Grothey et al. designed a randomized phase 2 trial whereby patients received either XELOX (N = 80) or XELIRI (N = 77) and upon progression were then treated with the alternative regimen: XELIRI (N = 34) or XELOX (N = 31). The doses for each 22-day cycle included capecitabine, 1,000 mg/m² twice daily on days 1 to 14; irinotecan,
Enter the Biologics

The next major advancement for CRC was the introduction of biologics, a form of targeted therapy. Bevacizumab is an antibody directed against VEGF, a soluble protein instrumental in angiogenesis. Use of targeted therapies in combination with cytotoxic agents is expanding options within the lines of therapy.

To determine whether the addition of bevacizumab to IFL improves survival among metastatic CRC patients, Hurwitz and colleagues randomly assigned 813 patients in a blinded fashion with previously untreated metastatic CRC to receive either IFL (the standard at the time) plus bevacizumab (N=402) or IFL plus placebo (N=411). A third arm included fluorouracil and leucovorin plus bevacizumab. After a predetermined interim safety analysis confirmed the safety of the IFL regimen with bevacizumab, the fluorouracil and leucovorin arm of the trial was discontinued. Patients received 5 mg/kg bevacizumab every 2 weeks. The primary endpoint was overall survival, and secondary endpoints were progression-free survival, response rate, duration of response, safety, and quality of life.

Adding bevacizumab to irinotecan plus bolus fluorouracil and leucovorin (IFL) resulted in a significant and clinically meaningful improvement in survival (20.3 versus 15.6 months; \( P < 0.001 \)). Median duration of therapy was 9.3 months in the arm receiving irinotecan plus fluorouracil and leucovorin plus bevacizumab and 6.4 months in the arm receiving irinotecan plus fluorouracil and leucovorin. The discontinuation rate due to adverse events was 8.4% in the irinotecan plus fluorouracil and leucovorin plus bevacizumab arm and 7.1% in the irinotecan plus fluorouracil and leucovorin arm. The incidence of any grade 3 or 4 adverse events was approximately 10% higher among patients receiving IFL plus bevacizumab than among those receiving IFL plus placebo; this was largely due to patients receiving the IFL plus bevacizumab regimen having higher incidences of grade 3 hypertension (11% versus 2.3%), as well as grade 4 diarrhea (32.4% versus 24.7%) and leukopenia (37% versus 31%).

In an abstract presenting a subsequent subgroup analysis, Hedrick et al. looked at use of irinotecan plus bolus fluorouracil and leucovorin plus bevacizumab followed by oxaliplatin second-line therapy. They found that irinotecan plus bolus fluorouracil and leucovorin plus bevacizumab followed by oxaliplatin second-line can prolong survival to 25.1 months. This subset analysis also suggests that a treatment strategy incorporating all active agents over the course of disease optimizes overall survival. Exposing patients to more active drugs, now including biologics, may push median survivorship even farther.

The Eastern Cooperative Oncology Group sponsored a trial for CRC patients who progressed after therapy with either fluorouracil or irinotecan plus fluorouracil. Patients were randomized to receive (1) bevacizumab plus FOLFOX4 or (2) FOLFOX4 alone or (3) bevacizumab alone. Response rate, progression-free survival, and overall survival were improved when bevacizumab was added to FOLFOX. The addition of second-line bevacizumab 10 mg/kg every 2 weeks to FOLFOX significantly improved median overall survival from 10.7 to 12.5 months. As a single agent, however, bevacizumab had minimal, if any, activity and therefore is not recommended as a therapeutic choice outside the clinical trial.

A randomized phase 2 trial by Hochster et al. added bevacizumab to oxaliplatin combination chemotherapy in patients with metastatic CRC. This randomized study assesses the safety and tolerability of each of 3 oxaliplatin plus fluoropyrimidine regimens (bolus, infusional, or oral fluoropyrimidine) alone in TREE1, and with bevacizumab in TREE2. Regardless of the chemotherapy employed, adding bevacizumab improved the response rate. These data with bevacizumab in colon cancer are consistent across trials and across chemotherapy regimens. The trial by Hochster et al. also suggested that the bolus fluorouracil/oxaliplatin regimen is inferior for patients with advanced colon cancer and cannot be recommended.

Clinicians need to monitor bevacizumab for its potential adverse events. There is a risk of bleeding, which often manifests as mild epistaxis. The risk of venous thromboembolism does not differ between the groups who received bevacizumab and who did not, so previous history of venous thrombosis does not preclude its use. Bevacizumab may be administered to patients who are anticoagulated for venous thrombosis. Proteinuria is a concern, as is hypertension, and must be monitored. The most recent warning for bevacizumab alerts clinicians to the possibility of reversible posterior leukoencephalopathy (RPLS), a condition similar to what is associated with malignant hypertension or eclampsia during pregnancy. Even mild hypertension or a change in blood pressure (e.g., from 90/60 to 120/85), can result in RPLS and will require discontinuing bevacizumab.

The risk of gastrointestinal perforation secondary to bevacizumab is rare, but real and potentially life threatening. It has been seen across trials. Episodes with or without intra-abdominal abscesses have occurred throughout treatment (i.e., they did not correlate with duration of exposure). Typical presentation was reported as abdominal pain associated with symptoms (e.g., constipation and vomiting). Bevacizumab therapy should be permanently discontinued in patients with gastrointestinal perforation.

Wound-healing complication (wound dehiscence) is also possible and is an important consideration in patients undergoing
surgery. Because of its long half-life, patients receiving bevacizumab-containing regimens must be bevacizumab-free for a minimum of 6 weeks before surgery. The risk of arterial thromboembolism is a concern, particularly for the elderly with a previous history of arterial thromboembolism, such as cardiovascular accident, myocardial infarction, transient ischemic attacks, or angina.46

One of the most significant findings in modern colon cancer therapy is that chemotherapy compared with best supportive care (BSC) is superior even when toxicity is considered. Two trials have also examined irinotecan as second-line therapy.67,68 A British study compared irinotecan to BSC prospectively; 279 patients with metastatic CRC who had failed fluorouracil therapy were randomized 2:1 to receive either BSC plus treatment with irinotecan 350 mg/m² every 3 weeks, or BSC alone. In the BSC group, 14% of patients were still alive at 1 year compared with the 36% of patients alive at 1 year after treatment with irinotecan (P=0.001).67 Patients receiving irinotecan lived significantly longer without performance status deterioration; and deterioration in quality of life (50% reduction from baseline) occurred significantly later in the irinotecan-treated patients than in controls.

Rougier and colleagues evaluated 101 patients randomized to receive 1 of 3 second-line regimens68:

- irinotecan 180 mg/m² on day 1 followed by a leucovorin 200 mg/m² infusion, before a fluorouracil 400 mg/m² bolus followed by a 5-FU 600 mg/m² infusion (LV5FU2 regimen), on days 1 and 2 every 2 weeks (N=35); or
- oxaliplatin 85 mg/m² on day 1 followed by the LV5FU2 regimen on days 1 and 2 every 2 weeks (N=33); or
- oxaliplatin 85 mg/m² followed by irinotecan 200 mg/m², on day 1 every 3 weeks (N=33).

Overall survivals were 12.2 months (95% CI, 9.2-16.0), 11.5 months (95% CI, 9.0-14.1), and 11.0 months (95% CI, 8.1-12.2), respectively. These researchers determined that second-line treatment with irinotecan/LV5FU2, oxaliplatin/LV5FU2, or irinotecan/oxaliplatin controls tumor growth well, increases survival, and is safe. The intention-to-treat objective response rates (ORRs) were 11.4% (95% CI, 3.2-26.7), 21.2% (95% CI, 9.0-38.9), and 15.2% (95% CI, 5.1-31.9), respectively, in the 3 arms. Tumor growth control was ≥60% for all 3 combinations.

**Cetuximab**

Cetuximab is a monoclonal antibody that specifically blocks EGFR. Cunningham et al. examined cetuximab’s efficacy in combination with irinotecan with that of cetuximab alone in metastatic CRC refractory to irinotecan.69 Patients (N=329) whose CRC progressed during or within 3 months of treatment with an irinotecan-based regimen were randomized to receive cetuximab plus irinotecan (N=218) or cetuximab monotherapy (N=111). The combination-therapy group was significantly more likely to respond than the cetuximab-alone group (22.9% versus 10.8%; P=0.007). Median time-to-progression was also significantly greater in the combination therapy group. The addition of irinotecan increased toxicity (i.e., diarrhea and neutropenia) as expected. Thus, cetuximab’s activity alone (unlike that of bevacizumab alone) or in combination with irinotecan was determined to be significant. Because this work is from phase 2 trials, we do not have survival statistics for cetuximab.

Cetuximab’s complete prescribing information indicates that cetuximab is appropriately used in tumors that stain positive for EGFR; however, neither EGFR-staining nor the percentage of cells expressing EGFR correlate with response rate.70 Furthermore, there are now data to support the use of cetuximab for EGFR-negative patients.71

With cetuximab and other EGFR-targeted therapies, skin toxicity may actually be a surrogate for efficacy. Trials have shown that those who develop the most pronounced acneiform rash are those who are most likely to benefit.72

Because cetuximab and bevacizumab have different toxicity profiles and biologic targets, theoretically it would be appropriate to look at cetuximab and bevacizumab combinations. A randomized phase 2 trial examined cetuximab and bevacizumab with or without irinotecan.73 The response rate was significant for patients receiving second-line or third-line treatment and superior for patients treated with the irinotecan-cetuximab-bevacizumab combination (38%, 8.5 months time-to-progression, compared with 23% time-to-progression for cetuximab and bevacizumab).

These data have stimulated the development of additional randomized phase 3 trials. It is now clear that second-line and third-line treatment can extend the benefit of first-line treatment. It increases response rates across treatment lines, extends overall survival using combinations of cytotoxic and targeted therapies, and appears to sensitize previously refractory tumors.

The challenge of these new regimens is that toxicity can be significant and patients grow weary of ongoing treatment. To address this problem, researchers are now examining “stop and go” approaches. One particular strategy drops the oxaliplatin after a defined period of time, introducing it again at disease progression.74 Initial studies suggest doing so is safe and uncompromising of the overall strategy. This suggests that at maximum response, patients might be afforded either complete breaks in therapy or less intensive therapy until the disease progresses. At progression, combination therapy can be reintroduced. This may alleviate toxicities and reduce costs.

The many choices for advanced metastatic CRC are reflected in the NCCN guidelines. NCCN has identified choices for people who cannot tolerate intensive therapy with agents such as capcitabine or infusional fluorouracil. For the less fit patient, it is important to weigh the risk of therapy, including combination therapy, with the need to achieve the best response as an effort to most effectively achieve disease control and improved performance status.
**Most Recent Approval: Panitumumab**

The FDA approved panitumumab in September 2006 (just a week before the symposium upon which the supplement is based). Panitumumab binds specifically to EGFR on normal and tumor cells, competitively inhibiting ligand-binding. After panitumumab binds to EGFR, ligand-mediated receptor site autophosphorylation is inhibited, as is activation of receptor-associated kinases. Cell growth is inhibited, and apoptosis is induced. Proinflammatory cytokines and vascular epithelial growth factor production decrease. Panitumumab differs from cetuximab, which is a chimeric antibody, in that it is a fully human monoclonal antibody. Some researchers believe that there is less risk for infusion reactions with fully human monoclonal antibodies.

Panitumumab’s pivotal trial was a phase 3 multicenter, randomized controlled trial. Peeters and colleagues compared the effect of panitumumab 6 mg/kg every 2 weeks and BSC (N = 231) with BSC alone (N = 232) in patients with progressive metastatic CRC during or following treatment with fluoropyrimidine, irinotecan, and oxaliplatin. All patients had at least 1% tumor cell membrane positive staining for EGFR by centrally read immunohistochemistry. Tumor responses were determined at weeks 8, 12, 16, 24, 32, 40, 48, and every 12 weeks thereafter until progression. Responses were confirmed more than 4 weeks after criteria were first met. This design is somewhat flawed in that people were allowed crossover and many patients had crossover before the first analysis. Patients receiving panitumumab plus BSC showed a significant improvement in progression-free survival, with a 46% lower relative progression rate versus the BSC-alone group. At as early as 8 weeks into treatment, a higher percentage of panitumumab plus BSC-treated patients were alive without progression than in the BSC group alone. This difference in favor of the panitumumab plus BSC group versus the BSC group alone continued through week 32 of the study.

**Conclusion**

Clearly, many choices are available to clinicians who treat patients who have CRC. They will need to balance concerns about toxicity with those about cost (see Table 4). In the coming months and years, the results from numerous ongoing clinical trials will further refine our choices. The experts at NCCN will continue to refine and update their guidelines to reflect these changes and to give patients the longest and best life after a diagnosis of CRC.

**DISCLOSURES**

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**TABLE 4** Estimated Drug Costs for 8 weeks of Treatment for Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs and Schedule of Administration</th>
<th>Drug Costs ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regimens containing fluorouracil</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>Monthly bolus of fluorouracil plus leucovorin</td>
<td>63</td>
</tr>
<tr>
<td>Roswell Park</td>
<td>Weekly bolus of fluorouracil plus leucovorin</td>
<td>304</td>
</tr>
<tr>
<td>LV5FU2</td>
<td>Biweekly fluorouracil plus leucovorin in a 48-hour infusion</td>
<td>263</td>
</tr>
<tr>
<td><strong>Regimens containing irinotecan or oxaliplatin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irinotecan alone</td>
<td>Weekly bolus of fluorouracil plus irinotecan</td>
<td>9,497</td>
</tr>
<tr>
<td>IFL</td>
<td>Weekly bolus of fluorouracil plus irinotecan</td>
<td>9,539</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>LV5FU2 with biweekly irinotecan</td>
<td>9,381</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>LV5FU2 with biweekly oxaliplatin</td>
<td>11,889</td>
</tr>
<tr>
<td><strong>Regimens containing bevacizumab or cetuximab</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFIRI with bevacizumab</td>
<td>FOLFIRI with fortinightly bevacizumab</td>
<td>21,399</td>
</tr>
<tr>
<td>FOLFOX with bevacizumab</td>
<td>FOLFOX with biweekly bevacizumab</td>
<td>21,033</td>
</tr>
<tr>
<td>Irinotecan with cetuximab</td>
<td>Weekly irinotecan plus cetuximab</td>
<td>30,790</td>
</tr>
<tr>
<td>FOLFIRI with cetuximab</td>
<td>FOLFIRI and weekly cetuximab</td>
<td>30,675</td>
</tr>
</tbody>
</table>

* Costs represent 95% of the average wholesale price in May 2004.


Medicare Challenges and Solutions—Reimbursement Issues in Treating the Patient With Colorectal Cancer

Kathleen Kaa, PhD, RPh

ABSTRACT

BACKGROUND: Medicare covers costs far more than 50% of all cancer patients, and most private payers follow Medicare’s lead on coverage and benefits for cancer care. Medicare and private payers are legally required by federal statute to cover anticancer chemotherapeutic products based on U.S. Food and Drug Administration-approved labeling and indicate how off-label uses are covered.

OBJECTIVE: To review reimbursement issues unique to Medicare with regard to oncology drugs.

SUMMARY: Currently, the Centers for Medicare & Medicaid Services (CMS) recognizes 2 compendia for purposes of evaluating off-label uses of drugs. Coverage determinations can be pursued nationally, locally, and case by case. Because of the impact and scope of colorectal cancer on the national budget, CMS initiated a process to establish national coverage determinations. This and other such Medicare reforms will have significant repercussions for clinicians who work with oncology patients. Major administrative and access challenges for both health care providers and beneficiaries include a diverse array of plan choices. In terms of Medicare Part D, the 25% of patients who are chronically ill and prescribed expensive therapies (including antineoplastics and supportive care agents) may find the coverage gap (“donut hole”) challenging and even prohibitive in their access to appropriate care. Lack of coverage could potentially affect therapy compliance, and managed care must pursue additional payment or coverage support mechanisms. Evaluating formularies will be critical for cancer patients and those who use specialty drugs as they select their Part D plans in the future.

CONCLUSION: Oncologists and their patients are left with difficult choices regarding not only the clinical efficacy of a treatment but also the financial considerations of the treatment.

KEYWORDS: Cancer therapies, Coverage gap, Medicare coverage, Medicare Part D, Medicare reform, Off-label prescribing

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edicare’s impact on managed care and the private market has dramatically increased as more payers offer coverage and care for Medicare beneficiaries through Medicare Part D. This growing influence has created new processes, prompting a push-and-pull interplay between public and private policies that is unlikely to resolve in the near future. The direct effects of public and private policies and practices appear to have reciprocal effects, more so today than in the past. This article will examine traditional Medicare coverage of cancer therapies, Medicare reform, Medicare Part D, and the implications of all of these for providers and cancer patients, with an emphasis on the differences in public and private approaches. Specific examples used will relate to colorectal cancer (CRC).

Previous articles have discussed infusion therapies and the brighter, more promising horizon for oral antineoplastics. Although the field of oncology will continue to rely on and welcome new infusion products, oncology practitioners are looking forward to the numerous oral products in the research pipeline. Managing existing and soon-to-be approved oral antineoplastics will create financial, administrative, and utilization management challenges in general, especially within the context of Medicare Part D.

The Burden of Colorectal Cancer

Medicare’s need to address CRC is largely based on the volume of patients affected; CRC is the second leading cause of cancer death in the United States. Because this disease generally affects people aged 50 years or older and the mean age at diagnosis is 72 years, most affected Americans are Medicare-eligible.1 As the “baby boomers” age, the number of and burden associated with Medicare-insured CRC patients will continue to rise. Hence, Medicare has been diligently working to establish a way to manage CRC appropriately, not only clinically but also financially, so that all beneficiaries have appropriate access to the improving standard of care. Medicare provides coverage for more than 50% of all cancer patients, and many private payers follow, or borrow significantly from, Medicare’s policies for coverage of and payment for cancer care.

Currently, Medicare is a significant payer for CRC (see Figure). It pays for 62% of costs associated with inpatient CRC care and 49% of all outpatient CRC care, of which 15% is provided in hospital outpatient departments and 85% in physician’s offices. Medicare’s typical beneficiary with CRC can be expected to be among the oldest and sickest of CRC patients.2 Discussion of Medicare in any context is often facilitated if the “parts” (e.g., the “entitled” Part A and the optional Parts B, C, and now D) are explained. Table 1 describes Medicare coverage.
In most cases, Medicare beneficiaries receive Part A coverage on a premium-free basis. Parts B, C, and D supplement Part A coverage and are optional benefits requiring separate premiums. Medicare’s regulations covering cancer are statute-based; if medically reasonable and necessary, Medicare must provide reimbursement for anticancer agents based on the agents’ U.S. Food and Drug Administration (FDA)-approved labeling. Statutory language in Section 1861(g)(1) and (2) of the Social Security Act provides Medicare reimbursement for off-label indications of products in chemotherapeutic regimens as well, and for off-label prescribing, a practice that is frequently used in the oncology field. The provisions are straightforward: the off-label use must be supported by 1 or more of the compendia listed in the statute, which are discussed further below, or the carrier involved must determine that the treatment is medically accepted based on peer-reviewed supportive clinical evidence appearing in publications as identified by the Secretary of the U.S. Department of Health and Human Services (HHS). Compendia are critical for applying Medicare’s off-label coverage policy because of how the statutory language defines its use. The importance of the compendia also extends to the private insurance industry. However, with significant variation among and within private payers, the private market does not use compendia in the consistent manner that Medicare does. Some private payers use compendia listings along with their own pharmacy and therapeutics reviews, which often include primary literature reviews, clinical data, and primary information from drug manufacturers.

Thus, to understand coverage policies for Medicare beneficiaires, health care providers often reference compendia listings or locate literature that supports the cancer diagnosis they are treating. The current Medicare-approved compendia include the United States Pharmacopeia Drug Information (USP-DI) and the American Hospital Formulary Service Drug Information (AHFS-DI). Medicare carriers generally use both compendia in their coverage decision-making processes and to confirm information found in each. It is important to note that a negative listing in one of the recognized compendia will trump a positive listing in another and potentially result in noncoverage.

In addition to the USP-DI and AHFS-DI, other compendia are petitioning to be included in Medicare’s list of approved compendia. One, the National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium, is becoming increasingly important. A nationally recognized group, NCCN is actively involved in creating and disseminating evidence-based and consensus guidelines for cancer care. This compendium delineates uses of drugs and biologics in the care of cancer patients, listing FDA-approved disease indications and specific NCCN recommendations for use as well as defining levels of evidence and categories of consensus-supporting recommendations. Other drug reference sources, including DRUGDEX System, the compendium used by Medicaid agencies, and Facts & Comparisons and Clinical Pharmacology, are also seeking formal recognition and CMS approval as part of the compendia process within the coverage determination.

Pathways to Coverage

CMS determines coverage for anticancer agents using 1 of 2 pathways: they make national coverage determinations (NCDs) or local coverage determinations (LCDs) through local CMS contractors. CMS will often use the NCD pathway if a technology, drug or biologic, device, or other medical entity is or will be a significant burden on the Medicare program. Factors like high patient volume or significant cost may influence a decision to develop an NCD to outline coverage provisions. CMS will also consider developing NCDs if treatment associated with a technology, drug, or device varies widely. In the case of CRC, clinicians and patients have the choice of numerous treatment options and therapeutic alternatives, and additional therapies are in pre-marketing stages of testing. Considering these reasons as well as the current and expected future burden of CRC on the Medicare system, it becomes clearer why Medicare elected to embark on
the NCD pathway for the management of CRC. This is discussed in detail below.

The second pathway to coverage, the LCD, is through local contractors who often subsequently post their decisions, which are based on either FDA-approved indications or the off-label rules described previously. Local contractors publicly post LCDs and coverage bulletins to their Websites for providers and patients to reference and understand coverage policies determined using this method. References based on previously reviewed requests for coverage are also used systematically to make case-by-case coverage determinations.

A History Lesson: CRC and CMS

The NCD process is quite involved and time-consuming; it takes months to years to complete, but the focus is to methodically evaluate evidence that will be used to develop consistent coverage policies for health technologies. Obvious and long-standing concern about CRC prompted CMS to open an NCD review process for oxaliplatin in February 2003. This was allowed under CMS’s authority to provide provisional coverage for products and therapies using the coverage with evidence determination (CED) protocol (which is discussed more thoroughly below). As additional medications became available to treat CRC, CMS expanded the scope of their NCD development efforts into the entirety of CRC rather than into 1 drug alone, and specifically into off-label uses of particular drugs within the CRC arena. They included irinotecan in the ongoing process in May 2003 and the biologics bevacizumab and cetuximab in September 2004.3

The FDA’s “Fast Track” designation process also addresses certain oncology products when the combination of a product and a claim reveal an unmet medical need. The FDA process also allows agents to undergo “Priority Review”—reducing the expected review time from 10 months to about 6 months—or “Accelerated Approval”—when a promising product is intended for life-threatening diseases. Hence, these products become available commercially on the basis of preliminary evidence prior to formal demonstration of patient benefit.6

Note that the FDA bases its decisions on safety and efficacy in product claims. CMS then accepts the FDA decisions to approve products before allowing them to come to market. However, CMS’s approval does not address its responsibility to provide coverage policies intended to ensure that products are used based on “reasonable and necessary” criteria. These are related yet different missions that the FDA and CMS own. CMS has a responsibility to provide beneficiaries access to the newest products and therapies, but it also has the responsibility of ensuring that adequate evidence exists to designate these therapies as “reasonable and necessary” within the conditions for treatment. At times, based on the speed of market approval and the populations in which products may have been tested as part of the FDA approval process, such evidence may be lacking (e.g., if agents navigate an expedited review process at the FDA).

As part of the NCD development process, and for the first time regarding drug therapy, CMS formally instituted and began providing coverage for products used in off-label situations while it evaluated clinical evidence; beneficiaries were granted coverage only if they were involved in clinical trials sanctioned by CMS. By doing so, clinical evidence was systematically and consistently collected and used to develop the NCD over time.

This process is a CED plan.7 CMS has applied CED plans previously; in all cases, the process made headline news. The first examined lung volume reduction surgery in patients with severe emphysema. The agency sought evidence to identify patients who would truly benefit from these surgeries. Others addressed the use of positron emission tomography scans for Alzheimer’s disease; bariatric surgery for patients older than 65 years; and expanding coverage of implantable cardioverter defibrillators. When Medicare uses the CED process to make coverage decisions, it is a burden in and of itself. Some concerns include the costs of the process, the provision of clinical trial medication data collection activities and analyses, and potential ethical repercussions of requiring participation in this clinical evidence collection process for coverage. These issues have and will continue to be discussed in public forums.

For CRC, the CED and NCD processes allowed for a large number of therapeutic options, and the milieu has been changing very quickly as more options continue to become available. In January 2005, after almost 2 years, CMS produced its NCD for off-label uses of CRC therapies. The NCD process is lengthy and, as in many diseases, the options for treating CRC are changing so quickly that taking 2 years for these review processes may be too slow. CMS and policy makers will continue to evaluate the need and utility of these processes, balancing them with the resources required.

The Changing Face of Medicare Part B

What has patient experience been as drug costs continue to rise? This is a question that has weighed heavily on all stakeholders’ minds over the last few years, and especially since Part D implementation. Patients have encountered some very difficult issues, and the market has responded in different ways.

In the United States, the issue of drug costs has recently taken on more policy significance. In 2006, CMS introduced the concept of basing provider-administered product reimbursement on average sales price (ASP). Until then, average wholesale price (AWP) was most commonly used to determine provider reimbursement for provider-administered products. CMS’s goal was to create a market-based approach to reimbursement with the presumption that this would decrease Medicare program spending. Specifically, the ASP-based formula has accomplished this. However, significant administrative issues still exist for providers. Are bona fide service fees included in ASP calculations? How is ASP calculated for newly approved medications? How should medications bundled together in contracts be
addressed? Clearly, further clarification about ASP calculations is necessary. These issues are crucial for providers since medication-based reimbursement is still a large part of their overall patient care equation. (See Update section.)

Many providers and provider groups have also reported that new administrative codes were not updated or adjusted in 2006. The resulting confusion led to inconsistent use of codes throughout 2006. Providers report that the Medicare claims payment process has been fraught with problems, and many carriers do not yet have the proper codes and payment rates loaded into their databases appropriately, even for 2006. These issues translate into problems for providers—payment cuts for drug product administration pursuant to ASP use and inaccurate claims payments for professional services. Clinicians and lobbyists continue to express concern, in many cases to Congress, that the cuts proposed for 2007 will further damage care coordination and complicate both patient care and office management issues that continue to place financial pressure on providers. (See Update section)

Their concern is valid. CMS announced changes proposed for 2007 in August 2006, and the comment period ended in October 2006. Many stakeholders have rallied against the proposed 5.1% reduction in the physician fee schedule; it is larger than predicted, and arguments have been made that it is inappropriate. Providers claim that this reduction will severely affect their ability to provide quality care to their patients. Additionally, CMS’s 1-year oncology demonstration project (a program to gather specific information relevant to cancer patients’ quality of care, including their treatments, the spectrum of care they receive from their doctors, and whether the care represents best practices) expires at the end of 2006. This could cost providers an additional $150 million in the reductions realized in 2006. The demonstration project helped minimize some of those financial effects of lower physician-office reimbursement for services, and provided incremental payment for medications and their administration to patients. What will follow, and the effects patients will experience, are now uncertain. (See Update section)

The issue of beneficiary out-of-pocket costs continues to be important—more so as patient out-of-pocket responsibilities increase. As prices for drugs increase, patient premiums, deductibles, and copayments also rise. For physician-office-based care, Medicare pays 80% of its allowable fee for office visits and medications administered by providers, leaving the remaining 20%, and the annual deductible, as the beneficiary’s responsibility. To illustrate how a 20% copayment can be burdensome for patients, consider an example of 1 CRC treatment: bevacizumab (340 mg) and 2 hours of infusion will cost the patient $497.49, plus their $124 annual Part B deductible and $88.50 monthly Part B premium. Note that the annual Part B premium becomes income-indexed in 2007.° Medicare pays $1,989.95 for the medication dose and administrative fee for giving the treatment. As these Part B-covered products are approved and reach the market with unprecedented price tags, intense scrutiny of Medicare benefits and medical costs will surely follow. The health care industry and the marketplace are now dealing with the burden of finding ways to ensure that out-of-pocket responsibility is not a barrier to health care access. (See Update section)

Medicare Part D

The basics of Part D are familiar to most managed care pharmacists by now. Beneficiaries have a diverse array of prescription drug plan (PDP) sponsors and Medicare-Advantage prescription drug (MA-PD) plan sponsors from which to choose. The available MA-PD plans offered in 2006 neared 1,900. As of June 2006, the HHS reported that 22.5 million beneficiaries had enrolled in Medicare Part D. Many chronically ill beneficiaries reach the “donut hole” during the third quarter of the year and thus will likely bear the full brunt of the coverage gap responsibility. (For all patients, Medicare covers 75% of the first $2,250 worth of drugs, but after that, coverage drops to zero and only resumes when the beneficiary reaches $5,100 in out-of-pocket expenses. Then, for most patients, Medicare pays 95% of costs. The approximately $3,000 gap in which patients must pay the entirety of drug costs is called the donut hole.) Because chronically ill patients typically have a profile that includes many medications, it is important to consider not only individual medications and their associated costs but also all medications and their collective costs in the donut hole conundrum. The vast majority of PDPs are not offering coverage through the donut hole in 2006. Individual plans’ sponsors have considerable latitude in this matter, however, and some plans do offer coverage. CMS data suggest that only 2% of plans cover branded and generic products and 13% cover only generic drugs through the donut hole.

The 2006 average monthly premium for beneficiaries enrolled in Part D was about $37, and it is likely to be slightly lower in 2007. Although experts expected that most plans would require a standard deductible of $250, only 34% of plans actually did. Many plans (58%) have no deductible. Note that this was quite different from what CMS provided as the model structure, knowing that individual plan sponsors had the autonomy to develop and provide plan designs that were actuarially equivalent to the standard structure.°

Specialty drugs deserve separate discussion, especially since many antineoplastics are considered specialty drugs. Most formularies have, until now, included specialty drugs and expensive therapies in the higher (third and fourth) tiers. That trend continued in Part D formularies, wherein more than 90% of plans have tiered structures and approximately 6% of drugs fall into the fourth tier. Much to the surprise of many, some Part D formularies specifically listed medications that are Part B-eligible. Medicare is in the process of issuing guidance for 2007, and it will include specific language concerning specialty products (e.g., products that have negotiated prices exceeding $500 per
month will be placed in a specialty tier and be covered with a coinsurance of 25% or less). This is the first time that CMS’s involvement has reached the level of telling plan sponsors how they must manage those products. Cancer patients will need to evaluate formularies very carefully as they select their 2007 Part D plan.

Many experts attempted to estimate how many beneficiaries would hit or surpass the donut hole in 2006. Medicare designed the donut hole as a risk management tool, so beneficiaries would share responsibility in their overall medication management costs. The Kaiser Family Foundation originally estimated in 2004 that 24% of beneficiaries would experience out-of-pocket spending within the donut hole. Recent figures, however, indicate that 35% of Medicare beneficiaries reached the donut hole by August 2006 and that of those, 16% would discontinue treatment all together. Patients who are on relatively inexpensive maintenance medications may not be as likely to feel the dramatic effects of this out-of-pocket responsibility, but those taking more expensive therapies such as oral cancer products are likely to reach the donut hole more quickly, some even as early as February.

Currently, as exceptions to Medicare law, Medicare Part B covers select oral antineoplastics, because they are considered prodrugs. For example, the fluorouracil precursor capecitabine is one of these Medicare Part B-covered drugs. Other products frequently used in the cancer population are provider-administered (e.g., injectables, infusables) and are Part B-covered, both as antineoplastics and supportive care products such as hemopoetic agents, antiemetic products, and some antinausea agents. It is important to note that cancer patients often have an armamentarium of other medications used in their overall cancer management plans, such as oral or self-administered therapies used for pain management and mental health. These agents play a significant role in the care of cancer patients, and they are not covered under Part B, but rather Part D.

In a 2004 editorial in the New England Journal of Medicine, Deborah Schrag, MD, summarized some of the cost concerns specifically related to CRC. She traced the progress of chemo-therapeutic agents from the 1960s, when fluorouracil was the primary chemotherapeutic agent available to treat CRC, to the 1990s, when the FDA began to approve what was then 5 new agents (irinotecan, oxaliplatin, capecitabine, bevacizumab, and cetuximab) for this indication. These therapies improved survival from a mean of 8 months without treatment to 12 months with fluorouracil. After 2002, median survival increased to 21 months with use of the newer agents, and lengthier survivals are expected as data from ongoing trials is collected. Doubling the median survival increased the cost of therapy 340 times, based on AWP—a staggering figure. Note that this figure does not account for the increased cost of simply living longer and being able to receive more cycles of therapy; it is based on an 8-week treatment plan. The cost of managing metastases and subsequent tumors is also not considered in this editorial comment. This is a very real example of how costs of care for CRC are increasing at rates that are significant and especially meaningful for patients as they are sharing the financial burden of receiving this care and, at times, with benefits that are being publicly debated.

As prices continue to rise, and life expectancy increases, Medicare CRC patients who lack supplemental coverage face tremendous financial challenges; they could accrue bills totaling 20% of the cost of treatment indefinitely based on therapies covered via Medicare Part B. According to Medicare Payment Advisory Commission (MedPAC), approximately 9% of Medicare beneficiaries have no source of supplemental coverage to alleviate this financial burden. Some physicians have continued to treat patients in their offices, despite the patients’ inability to meet the cost-sharing requirements. The result has been a financial liability for the practice. Costs associated with newer, innovative therapies will likely impact choices regarding therapy for cancer. Although newer therapies may have fewer side effects and improved remission and survival rates, the cost of care is considerably higher. Patients and the oncologists who treat them are left with very difficult decisions, including uncertainty about response to treatment that will mimic the efficacy rates in clinical trials and the high cost of the newer drug therapy options. Many practices, having incurred a liability by continuing to treat beneficiaries who cannot meet the cost-share, are beginning to counsel patients before treatment about the real or potential financial burden.

But increasingly, the concern is not only the uninsured but also the underinsured: patients who have coverage, but cannot afford their out-of-pocket responsibilities. Manufacturer-sponsored patient assistance programs have traditionally offered coverage to uninsured patients. More recently, copayment assistance foundations—bona fide, independent charities, often called “cost-sharing assistance models” or “copay assistance foundations”—have entered the health care milieu to provide assistance. CMS and the Office of the Inspector General have reviewed and endorsed this new model and developed a set of rules and guidelines by which these foundations must be developed and administered. These foundations do not provide drug-specific assistance but, rather, assistance across disease states without regard to specific products or manufacturers. Monetary donations from pharmaceutical manufacturers and other interested groups are pooled and designated for specific disease categories; patients with high-burden diseases then seek funding from this pool. Many foundations are focusing on CRC (Table 2) and finding ways to assist CRC patients with out-of-pocket requirements.

Summary

CMS, vis-à-vis the Medicare coverage process, is examining and implementing ways to continue providing access to therapies as the evidence about safety, efficacy, and effectiveness...
accumulates. Over time, public policy makers and Medicare will have to make decisions about the sustainability of the path they have chosen from financial, policy development, and overall burden standpoints. The private industry’s involvement in these processes will need to be assertive and forward-thinking, especially as expensive oral products become a more routine treatment choice. Patients’ out-of-pocket expenses will force our health care systems to look for ways to ensure continuing access to therapies and reduce financial burdens as a cause for nonadherence, therapy cessation, and changing treatment decisions by providers and patients.

**Update**

The following is information regarding developments since the October symposium relevant to the previous discussion.

**Medicare Physician Fee Schedule**

The Medicare Physician Fee Schedule (MPFS) final rule was released November 1, 2006. According to the final ruling, which became effective January 1, 2007, the Medicare program substantially increased work values for Evaluation and Management (E&M) Services—effectively reimbursing physicians more for the time they spend talking with Medicare beneficiaries about their health care. The ruling also mandated reimbursement for and measures to eliminate barriers for a broader range of preventive services, including exempting the cost of the colorectal screening from Part B deductible.

Although the December ruling was to implement a 5% cut in physician payments and reduce the conversion factor, Congress’s December 9, 2006, passage of the Tax Relief and Health Care Act overrode these directives, placing a moratorium on the cuts until the end of 2007.

The ruling maintained the current reimbursement rate of ASP+6% for Part B drugs administered in outpatient facilities. It did, however, clarify or address some outstanding ASP technical issues. New drugs are paid at 106% of the wholesale acquisition

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**TABLE 2** Copayment Assistance Foundations

<table>
<thead>
<tr>
<th>Program</th>
<th>Disease Areas *</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>
| HealthWell Foundation (www.healthwellfoundation.org) | - Chemotherapy-induced neutropenia  
- Myelodysplastic syndromes (MDS)  
- Non-Hodgkin’s lymphoma  
- Non-small cell lung cancer  
- Chemotherapy-induced anemia  
- Colorectal carcinoma  
- Multiple myeloma | (800) 675-8416 |
| NORD National Organization for Rare Disorders (www.rarediseases.org) | - Intrathecal therapy for pain management | (888) 744-2581 |
| PANF Patient Access Network Foundation (www.patientaccessnetwork.org) | - Breast cancer  
- Colorectal cancer  
- Cutaneous T-cell lymphoma  
- Non-Hodgkin’s lymphoma  
- Non-small cell lung cancer  
- Pancreatic cancer  
- Anemia  
- Chemo-induced nausea and vomiting  
- Oncology cytoprotection  
- Myelodysplastic syndrome  
- Multiple myeloma | (866) 316-PANF (7263) |
| PAF Patient Advocate Foundation (www.copays.org) | - Anemia/neutropenia secondary cancer treatment  
- Breast cancer chemotherapy  
- Kidney cancer  
- Colorectal cancer  
- Lung cancer  
- Lymphoma  
- Prostate cancer  
- Sarcoma | (866) 512-3861 |
| PSI Patient Services Incorporated (www.uneedpsiplatform.com) | - Chronic myelocytic leukemia | (800) 355-7741 |

* Not exhaustive list (see foundation Websites or call toll-free number for complete details)
cost (WAC) until price data is collected. CMS clarifies it will use the Medicaid definition of nominal sales—a price that is less than 10% of the average manufacturer price (AMP) in the same quarter for which the AMP is computed.

The CMS ruling did not finalize definitions for “bundled-priced concessions.” The December 2007 proposed rule regarding the calculation of AMP and best price reporting proposes to define the term “bundled sale” broadly as “an arrangement regardless of physical packaging under which the rebate, discount or other price concession is conditioned upon the purchase of the same drug or drugs of different types . . . or some other performance requirement . . . or where the resulting discounts or other price concessions are greater than those which would have been available had the bundled drugs been purchased separately or outside the bundled arrangement.”

Additionally, CMS proposes to require that discounts on bundled sales be allocated “proportionally to the dollar value of the units of each drug sold under the bundled arrangement . . . across all the drugs in the bundle.” CMS was accepting comments on the proposed rule through February 20, 2007.

Inconsistent Use of Administrative Codes

Recognizing a need to facilitate efforts toward consistent use of administrative codes, in November 2006, CMS and the National Center for Health Statistics released guidelines for coding and reporting using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The 102-page guideline document, developed in cooperation with the American Hospital Association (AHA) and the American Health Information Management Association (AHIMA), is intended to be used as a companion document to the official version of the ICD-9-CM as published on CD-ROM by the U.S. Government Printing Office. The guideline document is available online at http://www.cdc.gov/nchs/datawh/ftpserv/fiptcod9/icdguide06.pdf. The CMS Web site maintains a list of new, deleted, and revised codes available at http://www.cms.hhs.gov/ICD9ProviderDiagnosticCodes/07_summarytables.asp#TopOfPage.

Additionally, an official process for requesting new/revised ICD-9-CM procedure codes has been implemented and is available at http://www.cms.hhs.gov/ICD9ProviderDiagnosticCodes/08_ICD10.asp#TopOfPage.

Donut Hole

Beginning January 1, 2007, beneficiaries reaching the donut hole became responsible for $3,850 in out-of-pocket total drug spending until the Medicare drug benefit begins covering 95% of costs. This represents a slight increase over the 2006 required total $3,600 drug spending.

A study by the Kaiser Family Foundation investigating the impact of the donut hole on Medicare beneficiaries during 2006 found that nearly half of all Medicare beneficiaries, or 10.9 million people, were enrolled in plans that made them responsible for 100% of their drug spending when reaching the donut hole, and approximately 4 million beneficiaries had drug spending in 2006 inside the coverage gap. Only about 12% of those beneficiaries had drug plans that helped with costs inside the donut hole, and about 60% of these beneficiaries had plans that covered only generic drugs. Of 266 companies offering donut hole Medicare drug plans in 2006, 10 accounted for 72% of the market.

In 2007, 85% of plans are offering comprehensive coverage, which includes the so-called donut hole coverage gap. Still, most (about 85%) of these plans providing gap coverage only cover generic drugs. And the average generic-only gap coverage monthly premium is $51.11 compared with the no-gap policy premium of $30.17. Brand/generic gap coverage premiums soar more than 3-fold higher than the no-gap coverage at $93.46.

More recent attention has been on the societal implications of the generic-only provisions of private insurance “gap” coverage. Some beneficiaries, such as those with multiple sclerosis or rheumatoid arthritis, must take brand-name drugs because there are no generic alternatives. Las Vegas-based Sierra Health Services, the only major plan to cover brand-name drugs in the “gap” this year, reportedly lost $3 million in the first month of operation and was forced to cease its brand-name coverage option for 2008. Humana had a similar experience in 2006 when it tried to cover brand-name drugs in its gap policy. These experiences are only likely to reinforce plan decisions to circumvent the societal need for expanded gap coverage formularies in certain patient populations.

Oncology Demonstration Project, Pay-for-Performance-Based Fee Bonuses

CMS’s oncology demonstration project was not extended for 2007. At the time the project’s discontinuation was announced, chief among the concerns was the loss of millions of dollars in compensation it has provided to physicians over its 2-year tenure. In this regard, CMS is counting on bonus payments to physicians who meet and report certain quality measures from July 1, 2007, to December 31, 2007, provided for in the Tax Relief and Health Care Act of 2006 (HR 6111) through the 2007 Physician Quality Reporting Initiative (PQRI).

Those physicians who satisfactorily submit data will receive a payment equal to 1.5% of all allowed charges for the period between July 1, 2007, and December 31, 2007, subject to a cap. An aggregate dollar amount of $1.35 billion is the limit for 2008. The payment for 2007 will be a 1-time, lump-sum, after-the-fact payment. Claims may be submitted through the end of February 2008 for services rendered during the reporting period and the payment will not be forthcoming until after that time.

REFERENCES


Colorectal Cancer: Complexities and Challenges in Managed Care

Neil B. Minkoff, MD

ABSTRACT

BACKGROUND: Managed care weighs advances and associated costs to determine whether the combination of longer life at sometimes significantly increased cost represents value. The price of treatment is only 1 factor.

OBJECTIVE: To review treatment decision processes for oncologic agents in managed care environments.

SUMMARY: Price can be exceptionally high for individuals. But if the population size is low, the per-member-per-month (PMPM) impact can be almost negligible, unlike treatments that have moderate costs but are used ubiquitously. Cancer therapies have, for the most part, escaped managed care’s notice. For 2007, the National Cancer Institute projects that antineoplastic agents will consume almost a quarter of the overall drug spend. The Medicare population is a unique concern with regard to cancer. Traditionally, Medicare reimbursement of chemotherapeutic agents was based on average wholesale price (AWP) discounting, not the oncologist’s purchasing cost. This allowed oncologists to use reimbursement for infusions to support their medical practices. The proposed plan of the Center for Medicare & Medicaid Services (CMS) to use average sales price (ASP) plus 6% to reimburse for drugs used in the office setting leads to significant problems. Pharmacy and therapeutics committees will also face challenges: fewer data are available for some agents because they have become available through the U.S. Food and Drug Administration’s Fast Track, Priority Review, or Accelerated Approval processes.

CONCLUSION: Oncology disease management programs must reach out to patients and not necessarily deal with oncology issues directly, but address tangential issues that impact care, especially depression and pain management.

KEYWORDS: Accelerated Approval, Antineoplastics, Colorectal cancer, Fast Track, Medicare, Priority Review, Reimbursement

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 Remarkable advances in oncology therapy have created significant improvements in survival and often decreased chemotherapy-induced toxicity. Associated with these advances is a cost. Managed care must always weigh advances and their associated costs to determine if the combination represents value. In addition, managed care administrators must develop treatment decision processes and coverage policies. Doing so is rarely easy.

Cancer researchers usually look at 2 endpoints when they investigate new therapies: time-to-progression and survival. They are not usually concerned with cost. Work published in 2004 in the New England Journal of Medicine, however, did look at the escalating cost of cancer care and its relationship to survival. With no therapy prior to the 1960s, patients who had metastatic colorectal cancer (CRC) could be expected to survive approximately 8 months. Adding single therapy with fluorouracil in the mid-1960s increased median survival to about 1 year. When combination therapy (fluorouracil plus leucovorin plus oxaliplatin, FOLFOX) was approved by the U.S. Food and Drug Administration (FDA), survival lengthened to 21 months. The newer biologic agents (FOLFOX plus bevacizumab) increased survival further, so that patients with metastatic CRC routinely survive for 2 years. The doubling of immediate survival came about with a 340-fold, or greater than $21,000, increase in drug cost for the initial 8 weeks. Regardless, this may be a good return on investment, because now survival is measured in years as opposed to months.

Despite the magnitude of the increase in sheer cost, the actual budget impact in managed care has continued to be relatively small. The price of treatment is only 1 factor that managed care must weigh. That price can be exceptionally high for individuals, but the population size is remarkably low, creating a per-member-per-month (PMPM) impact that is sometimes almost negligible—unlike treatments that have moderate costs but are used ubiquitously, such as statins, antidepressants, and proton pump inhibitors. Treatment duration has tended to be reasonably short. Using these agents also offsets other costs, by eliminating the need for surgery or decreasing hospitalization or length of stay, and their incremental benefits are elusive. Thus, cancer therapies have escaped managed care’s aggressive notice.

Much of managed care’s difficulty with antineoplastics and cancer is that managed care administrators tend to lump all costs together for many disease states and cancer in particular when, in reality, cancer is a group of diseases. Managed care is adept at tracking silo costs related to pharmacy, laboratory, and medical budgets and costs. Defining costs by disease state is much more unusual and difficult, and is a hindrance, because doing so eliminates an appropriate context in which to make budgetary decisions. Optimally, coverage decisions should be determined for disease states as opposed to individual pharmaceuticals. For
plans that have significant pharmacy carve-out, the challenges are greatest.

An additional confounder is the change in the way the Centers for Medicare & Medicaid Services (CMS) plans to reimburse for Medicare, with an eye toward reducing its costs. Traditionally, Medicare reimbursement was based on actual wholesale price (AWP) discounting, not the oncologist’s purchasing cost of the chemotherapy agent. This allowed oncologists to use reimbursement for infusions to support their medical practices. In all fairness, the margins on these products could be significant because the fee schedule was constructed irrationally. Oncologists might be underpaid for clinical work, but overpaid for drug administration, leading to a kind of balance. Therefore, a change in one reimbursement type tends to lead to changes in the other.

Medicare’s proposed plan is to use average sales price (ASP) plus 6% to reimburse for drugs used in the office setting. However, that in and of itself leads to significant problems. Thus, CMS initiated demonstration projects to mitigate the extreme decrease in aggregate oncology reimbursement. Some people knowledgeable about CMS demonstration projects indicate that they were designed as temporary bridges to alleviate oncologists’ cash flow problems pursuant to the impact of the ASP plus 6% plan—a decrease in physician reimbursement from $130 per patient per day in 2005 to $23 per visit in 2006 for reporting data as part of the demonstration project. Others indicate that the demonstration projects are proof that Medicare knows that they can’t change the system significantly, and they are using these project to ensure that clinicians are paid adequately. The reality is probably somewhere between these 2 extremes, but the change is important because, in oncology, medications are crucial.

Antineoplastic agents accounted for 16% of the total dollars spent on medications in the United States in 2004. For 2007, the National Cancer Institute projects that antineoplastic agents will consume almost a quarter of the overall drug spend. The Pharmaceutical Research and Manufacturers of America reports that, in 2005, there were 399 chemotherapeutic agents in development. Thus, chemotherapeutic agents accounted for half of all drugs in development, and 35% of the agents being tested were formulated as oral agents. This is attracting a tremendous amount of attention, especially among investors. Additionally, media is making the cost of these agents into leading stories, and one story premise is that when insurance companies have difficulty managing or deny access to an agent, the manufacturer can set virtually any price.

This means that managed care pharmacy departments must become involved in some decisions regarding oncology care. This is a new phenomenon. Pharmacy has not been concerned with traditional chemotherapy because it was primarily given parenterally and covered by Medicare Part B as opposed to Medicare Part D. Instead, chemotherapy has traditionally been a concern for physicians’ offices and hospitals. The advent of oral agents is changing the reimbursement structure, and managed care pharmacy will need to integrate new agents with the older medications and create comprehensive coverage. The difficulty is that this is a very emotional subject because of the life-threatening nature of CRC, and the advocates for increased availability of new treatments regardless of cost or evidence form a strong lobby. Advocates will scrutinize efforts to manage cancer drugs, and the amount of feedback and comment tends to be disproportionate compared with the number of patients actually affected.

Pharmacy and therapeutics (P&T) committees will also face challenges as they try to develop rational formularies. Fewer data than usual are available for some of these agents because they have become available through the FDA’s Fast Track, Priority Review, or Accelerated Approval processes. Many agents’ approvals may be based on surrogate endpoints rather than clinical outcomes. With combination therapy increasingly more prevalent for CRC, new agents replace older drugs; they augment them, and provide no cost offset whatsoever. When alternatives can be offered, patient satisfaction remains high. With only a limited number of products FDA-approved to treat CRC, it is impossible to select preferred agents. Similar or generic products are not available as substitutes.

Cost and Survival

Returning to the opening example of a 2-fold increase in median survival for metastatic CRC compared with a 340-fold increase in cost, this can translate into considerable budgetary impact. And, in other types of cancer, similar situations have developed. Imatinib, for example, increased survival in chronic myelogenous leukemia significantly. The 3-year survival rate is 95% compared with 68% to 70% previously. Its monthly cost, however, ranges from $3,082 to $6,164, depending on the dose employed. Other examples are more striking. Sorafenib, recently approved for advanced or metastatic renal cell carcinoma, increased survival from a mean of 84 days using placebo in patients who had failed previous treatment to 167 days. (No agent was considered standard of care in this cancer prior to sorafenib’s approval, which is why the FDA allowed a placebo-controlled trial.) One can look at this as doubling survival or that the survival is still only 83 days. The cost of therapy for an additional 83 days of life is $28,000. Extrapolating the cost to months and years leads to an enormous cost estimate.

Finally, erlotinib was approved for non–small-cell lung cancer, offering a median increase in survival of approximately 2 months—from 4.7 months with placebo and traditional therapy to 6.7 months with erlotinib and traditional therapy. The cost of that extra 2 months of survival equates to slightly more than $14,000. Our systems will have to absorb these new costs.

Creating Context

Managed care is beginning to establish a benchmark describing the quality-of-life-per-year cost in terms of cost-effectiveness. For
example, a new product, panitumumab, was approved for the treatment of metastatic CRC in patients who have progressed on standard chemotherapy. This drug, like many others, was fast-tracked based on the results of a trial of only 463 patients. Survival was similar in both the treatment and control groups, but the mean time to progression was 36 days longer for patients treated with panitumumab. Its actual pricing is approximately $2,000 per week. Pharmacy departments or response managers must not approach the cost of therapies for cancer in a vacuum, and should develop a context within which cost is one element of a larger picture. These costs are high relative to some issues; $14,000 to extend life for 2 months is not excessive compared with the costs of a hospital stay, a major surgery, home care, or things of that nature. Appropriate benchmarks should be other types of care given to these patients, which is part of the overall cost of cancer. Managed care has room for improvement in evaluating the cost of care in general, and cancer in particular. Our approach to end-of-life issues is awkward; we prefer to discuss quality-of-life issues. One way to improve quality of life for terminal cancer patients is good pain management. Benchmarks for pain management should encourage cancer patients to manage pain effectively at home. Better antineoplastics are also needed; they should be less toxic than previously used agents and offer longer survival. Quality of life, however, will only be sustained if patients can access other services during that time span. Otherwise, the months of additional survival are of poor quality, representing a bad outcome for all involved.

Oncology disease management programs must reach out to patients and not necessarily deal with the oncology issues directly, but address the tangential issues that impact care, especially depression and pain management. P&T committees must not contemplate the issues and make decisions in a vacuum; many of these decisions are societal issues concerned with determining the value of new therapies monetarily and otherwise. In this respect, American society differs from other cultures. For example, in the United Kingdom, combination therapy is not first-line for CRC; fluorouracil is. If progression occurs, combination therapy is likely the next step. Americans have not collectively made a single decision about how CRC will be managed; individual care providers make the decisions. Serious national debate is needed on issues like this, and Medicare’s efforts are a first step in that direction. A more intricate framework or matrix would help us evaluate these kinds of products in terms of the costs society is willing to bear. Developing and using a better framework would remove insurance companies, employers, patients, pharmacies, and individual oncologists from the debate of what priorities should be and where our efforts are best placed. Unless Americans unite and deal with these issues, individuals will continue to have to sort through a tremendous number of problems with little guidance.

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REFERENCES
Targeted, Evidence-Based Colorectal Cancer Therapies: Shifting the Patient Outcome

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Posttest Worksheet: Targeted, Evidence-Based Colorectal Cancer Therapies: Shifting the Patient Outcome

1. Which of the following statement(s) are true?
   1. Globally, CRC is an uncommon cancer.
   2. Most cases of CRC are familial.
   3. In the United States, CRC is the second most common cancer in men and women and has a 5-year mortality rate of 40%.
   4. Age is unrelated to risk for colorectal cancer.
   a. 1 and 3
   b. 2 and 4
   c. 3 only
   d. None of the above are correct

2. Identify the site at which 70% of CRC patients will eventually develop metastases:
   a. Bone
   b. Liver
   c. Lung
   d. Brain
3. Which of the following statements is false?
   a. Diet is a leading risk factor for CRC.
   b. High-fat diets, inactivity, obesity, smoking, and alcohol use increase your risk for CRC.
   c. Patients with FAP inevitably develop colorectal cancer.
   d. CRC develops at an early age in FAP patients, but it can be prevented by educating the patient.

4. What gene mutations have been identified in the abnormal proliferation of cells that enable development of CRC?
   a. APC  
   b. MMR  
   c. K-ras  
   d. p53  
   e. All of the above

5. Which of the following statements about screening is false concerning CRC?
   a. Recommendations support screening or all men and women older than 50 years.
   b. People identified with genetic predisposition to CRC who have had first-degree relatives with early CRC should be screened by colonoscopy every 2 years starting at age 40.
   c. Colonoscopy remains the gold standard for screening and diagnosis.
   d. Flexible sigmoidoscopy may be done every 5 years but must be coupled with fecal occult blood testing annually.

6. What tumor status is associated with the highest 5-year survivorship for surgical resection in patients with Stage II metastatic CRC with no lymph node involvement?
   a. T4 low grade  
   b. T3 high grade  
   c. T3 low grade  
   d. T4 high grade

7. Which of the following statements is true about therapy for CRC patients since 2000 when the effectiveness of irinotecan was established?
   a. The focus has shifted away from curative patients in the adjuvant setting to metastatic patients in the neoadjuvant setting.
   b. The choices of drug regimens has changed very little.
   c. The number of cytotoxic agents used in a drug regimen has not been related to overall survivorship.
   d. All of the above are false

8. Oxaliplatin-containing CRC regimens of chemotherapy have been statistically more effective than capecitabine-containing regimens.
   a. True  
   b. False

9. In trials of first-line CRC chemotherapy combined with bevacizumab, which of the following were not observed?
   a. Overall survivorship persisted over time, with 50% survivorship increasing from 15.6 months to 20.3 months with the addition of bevacizumab.
   b. Bevacizumab regimens demonstrated higher Grade 3 and 4 adverse events.
   c. The risk of venous thromboembolism was higher with the addition of bevacizumab.
   d. All of the above were observed

10. Because of its long half-life, patients receiving bevacizumab-containing regimens must be bevacizumab-free for a minimum of 6 weeks prior to surgery.
    a. True  
    b. False

11. Which of the following statements is false?
    a. Cetuximab and bevacizumab have different toxicity profiles and biologic targets thus both are being studied in combination in CRC patients.
    b. Panitumumab is similar to cetuximab except that it is a fully humanized monoclonal antibody and cetuximab is a chimeric antibody.
    c. Bevacizumab dose reductions are recommended in patients who experience GI perforation.
    d. As a single agent in CRC, bevacizumab has minimal, if any, activity.

12. Medicare’s need to address CRC is based on all of the following except:
    a. CRC is the third leading cause of death.
    b. Most CRC patients are Medicare eligible because the median age at diagnosis is 72.
    c. The number of cases and burden associated with Medicare-insured CRC will increase.
    d. All of the above are true

13. Who are the major payers for colorectal cancer?
    a. Private payers  
    b. Medicaid  
    c. Medicare  
    d. Self-pay/other
14. Which of the following statements is true about Medicare’s evaluation of off-label use of drugs for reimbursement decisions?
   a. Medicare will provide reimbursement for off-label use according to P&T Review Committees.
   b. The off-label use must be supported by the United States Pharmacopeia Drug Information (USP-DI) or the American Hospital Formulary Systems Drug Information (AHFS-DI).
   c. The off-label use must be supported by United States Pharmacopeia Drug Information (USP-DI), the American Hospital Formulary Systems Drug Information (AHFS-DI), NCCN Drugs and Biologic Compendium, or DRUGDEX.
   d. Medicare carriers recognize only one compendia to determine “medically necessary” in their coverage decision-making processes for off-label uses.

15. Which of the following drug reference resources is not being petitioned to be included in Medicare’s list of approved compendia?
   a. American Cancer Society’s Treatment Guidelines
   b. NCCN Drugs and Biologics Compendium
   c. DRUGDEX System
   d. Facts and Comparisons

16. Which of the following statements is true?
   a. The focus of the national coverage determinations (NCD) is to make case-by-case coverage determinations based on previously reviewed requests for coverage.
   b. The focus of the NCD is to systematically evaluate evidence that will be used to develop consistent coverage policies for health technologies.
   c. The majority of coverage decisions are made by CMS.
   d. It is not CMS’s responsibility to ensure that adequate evidence exists to designate therapies as “reasonable and necessary” with the conditions for treatment.

17. Which of the following statements about Medicare Part B or D is false?
   a. Medicare Part B must cover an oral chemotherapeutic agent if it is considered a prodrug.
   b. Medicare Part B covers the approved provider-administered infused chemotherapy agents.
   c. Medicare Part B covers chemotherapeutic supportive therapies if they are intravenous and subcutaneous injectable agents, but not if they are oral agents.
   d. Medicare Part B covers all supportive therapies regardless of their indications.

18. Which of the following has been an effect of the cost for newer, innovative therapies for CRC?
   a. Higher usage of long-term oncology and supportive therapies
   b. Patient choices about whether to comply with, continue, or initiate therapy
   c. The development of charitable Copayment Assistance Foundations
   d. Physician choices for medical management of the oncology patient
   e. All of the above have been a result of the costs of newer innovative therapies for CRC patients

19. What is the most recent estimate of patients with no source of supplemental coverage, according to 2006 testimony presented by the Medicare Payment Advisory Commission (MedPAC)?
   a. 9%
   b. 19%
   c. 32%
   d. 65%

20. The Office of the Inspector General (OIG) guidelines allow Copayment Assistance Foundations aimed at assisting patients with access to specific drug or medical product manufacturers.
   a. True
   b. False

21. The availability and use of combination therapy—and specifically FOLFOX, a 5-FU/Irinotecan/oxaliplatin combination—lengthened the survival of colorectal cancer to
   a. 6 months.
   b. 12 months.
   c. 15 months.
   d. 21 months.

22. The newer biologic agents doubled survival in metastatic CRC patients; however, this was associated with an increase in drug cost for the initial 8 weeks of therapy of what magnitude?
   a. 10-fold
   b. 250-fold
   c. 340-fold
   d. 520-fold
23. Which of the following statements is true?
   a. Cancer therapies have escaped managed care’s aggressive notice previously because of their lower incremental impact on budget compared with other more chronic illnesses that affect larger populations.
   b. Antineoplastics accounted for 5% of the total dollars spent on medications in the United States in 2004. In 2007, the National Cancer Institute projects that antineoplastic agents will consume almost half of the overall drug expenditures.
   c. The Pharmaceutical Research and Manufacturers of America reports that in 2005 there were 550 chemotherapeutic agents in development.
   d. All of the above statements are true

24. Pharmacy & Therapeutics Committees will face challenges as they try to develop rational formularies for cancer therapies for all of the following reasons except:
   a. A limited number of products prevent the option of providing replacements or drug tiers.
   b. Fewer data than usual are available for some of these agents because they have become available through the FDA’s Fast Track, Priority Review, or Accelerated Approval processes.
   c. The newer agents are given in combination with older drugs to augment therapy, thus providing no cost offset whatsoever.
   d. All of the above statements are true

25. Presently, P & T Committees consider the societal issue related to the overall cost of cancer to decide their responsibilities for the cost of care.
   a. True
   b. False

26. A framework matrix for the health care system— including insurance companies, employers, patients, pharmacies, and the oncologists—to evaluate the direction of future priorities, efforts, and investments for the cost of products and cost for oncology care should consider which of the following factors?
   a. Actual gains in survival
   b. Improvements in quality of life
   c. Palliative benefit
   d. Budgetary impact
   e. All of the above

27. Which of the following is not true about panitumimab’s approval for the treatment of CRC?
   a. It was approved in September 2006.
   b. Its approval was fast-tracked by the FDA.
   c. Its approval was based on the results of preliminary results of a Phase IV multicenter randomized trials of more than 1,500 patients.
   d. Its approval was based on findings that the mean time to disease progression was 36 days better for patients getting panitumimab.