Strategies for Treating Colorectal Cancer

At Various Stages

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INTRODUCTION

Colorectal cancer is a significant contributor to morbidity and mortality in the U.S., making this disease the second leading cause of cancer deaths overall. In 2002, more than 56,000 people in the U.S. died of colorectal cancer (28,471 men; 28,132 women). Studies published in the early 1990s showed that screening could reduce colorectal cancer–related mortality; this finding has prompted many organizations to recommend screening in asymptomatic, average-risk adults older than 50 years of age.

Although screening rates are beginning to rise, they remain too low to achieve the Department of Health and Human Services’ Healthy People 2010 objective for reducing mortality rates from colorectal cancer. In 2004, approximately 57% of adults aged 50 years or older reported that they received a fecal occult blood test (FOBT) or a lower endoscopy examination within one year of being surveyed by CDC’s Behavioral Risk Factor Surveillance System, compared with 54% of adults surveyed in 2002.

Colorectal cancer takes approximately equal numbers of lives of both men and women each year. Mortality rates for colorectal cancer have declined for men since 1985 and for women since 1950. This decreased incidence and mortality rate is largely a result of detection and removal of precancerous polyps, early detection of tumors through screening, and improved treatments.

PATHOGENESIS

The etiology of colorectal cancer is complex and appears to involve interactions between inherited susceptibility and environmental factors. Most colorectal cancers are thought to develop from benign precursor lesions, or adenomatous polyps, which may vary from tiny nodules to tumors up to 12 cm in diameter. These cancers can arise in a pre-existing adenoma or de novo, but the relative importance of these two pathways is unclear. Colorectal cancer develops from areas of dysplasia. Adenomas and carcinomas often coexist, and adenomatous remnants are frequently found in carcinomas. De novo cancers, however, have been observed to arise in flat mucosa, and flat elevated cancers may originate from a pathway that differs from the adenoma–carcinoma sequence.

Adenomatous polyps are benign tumors that develop on the lining of the bowel. Some become malignant over time. Most evidence suggests that adenomas are precursors for a substantial proportion of colorectal cancers. This has prompted considerable interest in removing adenomas to prevent the development of colorectal cancer. Between 70% and 90% of colorectal cancers arise from adenomatous polyps, and 10% to 30% arise from sessile adenomas. The larger the polyp, the greater the potential for malignancy.

Diminutive polyps (5 mm or less in diameter) have a negligible malignant potential. Polyps with a diameter of 5 to 10 mm are considered small, whereas polyps greater than 10 mm in diameter are considered large. Polyps larger than 2 cm in diameter have a 50% chance of becoming malignant over time.

DIAGNOSIS

The American Cancer Society has recommended the following screening protocol for people at normal risk older than 50 years of age:

- a yearly fecal occult blood test to detect microscopic blood in the stool
- flexible sigmoidoscopy at age 50 for direct visualization of the colon lining via a sigmoidoscope or an endoscope
- flexible sigmoidoscopy, repeated every five years
- double-contrast barium enema every five years to show the contour of the lining of the colon; a white contrast image of the lining is visible on x-ray film
- colonoscopy of the entire colon every 10 years

In 2003, the American Gastroenterological Association revised its screening guidelines as follows:

- People with two or more first-degree relatives with colorectal cancer or a first-degree relative with colon or rectal cancer before age 60 should have a screening colonoscopy beginning at age 40 or beginning 10 years prior to the age of the earlier colon cancer diagnosis in the family (whichever is earliest).
- People with a first-degree relative who had colon cancer after age 60 or with two second-degree relatives who had colon or rectal cancer should begin screening at age 40 with one of the methods listed earlier, such as annual sigmoidoscopy.

STAGING

The prognosis of patients with colon cancer is related to the degree of penetration of the tumor through the bowel wall, the

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TREATMENT

Surgery for Colon Cancer

Surgical removal of the involved segment of colon (colectomy), along with its blood supply and regional lymph nodes, is the primary therapy for colon cancer.25 The conventional and accepted treatment for curative resection of colon cancer is laparotomy with hemicolectomy for right-sided or left-sided lesions.25

The technique of colon resection through an open laparotomy incision is well known. Over the past several years, laparoscopy-assisted colectomy has been developed. Laparoscopic surgery can be used for safe and radical resection of cancer in the right, left, and sigmoid colon.26

Usually, partial colectomies can be performed in the right, left, transverse, or sigmoid sections, according to the blood supply. The removal of the blood supply at its origin, along with the regional lymph nodes that accompany it, ensures an adequate margin of normal colonic tissue on either side of the primary tumor. When the cancer lies in a position such that the blood supply and lymph drainage are between two of the major vessels, both vessels are removed to ensure complete radical resection (an extended radical right-sided or left-sided colectomy).

If the primary tumor penetrates through the bowel wall, any tissue adjacent to the tumor extension is also removed if feasible.

The right, left, or sigmoid colon can be mobilized, and regional lymphadenectomy is performed with laparoscopic instruments and video-imaging equipment. The advantage of laparoscopic colectomy is the abdominal port site and the wound incisions can be small, resulting in less postoperative pain and analgesia, an earlier return of bowel function and normal physical activity, and a shorter hospital stay without increased health care costs.25

Surgery is the primary therapy for stages I through III colon cancer unless signs indicate that local invasion would not permit complete removal of the tumor. Although this situation sometimes occurs in advanced stage III tumors, this circumstance is rare, occurring in fewer than 2% of all colon cancer cases.

Radiation Therapy for Rectal Cancer

Published randomized trials suggest that radiation, before or after surgery, appears to have a significant impact on local recurrence, although it does not increase survival rates. Physicians recommend radiation therapy as an adjunct to surgery if there is a concern about the potential for local recurrence postoperatively and if the area of concern can tolerate the
Adjuvant Chemotherapy for Colorectal Cancer

Several disadvantages:

- Downstaging of the tumor is possible.
- Resectability of the tumor is increased, possibly with a sphincter-sparing procedure.
- The tumor is less viable, and this may decrease the risk of local recurrence.
- Less radiation is needed for small-bowel loops, which result from pelvic adhesions postoperatively.
- Radiation before surgery works better in well-oxygenated tissues; after surgery, tissues are relatively hypoxic and may be more resistant to radiotherapy.
- Adjuvant therapy may be delayed in patients with postoperative complications.

However, preoperative radiation therapy is associated with some disadvantages, such as (1) a delay in definitive resection, (2) the possible loss of accurate staging, (3) possible overtreatment of early-stage (I and II) rectal cancer, (4) increased postoperative complications, and (5) higher morbidity and mortality rates secondary to radiation injury. Although preoperative radiation decreases the risk of tumor recurrence in patients with stage II or III disease, this practice does not lead to a decrease in distant metastases or in a higher survival rate. Some reports cite an increase in survival, but this does not lead to a decrease in distant metastases or in a higher recurrence in patients with stage II or III disease, this practice

Postoperative Radiotherapy

Advantages of postoperative radiation therapy include (1) immediate, definitive resection and (2) the ability to obtain accurate information on staging of pathology before ionizing radiation is begun. However, this technique is associated with several disadvantages:

- Adjuvant radiation therapy may be delayed if postoperative complications follow.
- There is no effect on tumor cell spread at the time of surgery.
- The effect of radiation is decreased in surgically induced tissue hypoxia.

Adjuvant Chemotherapy for Colorectal Cancer

Single-Agent Regimens

5-Fluorouracil. It has been 50 years since the introduction of 5-fluorouracil (5-FU) in the treatment of colorectal cancer. The fluoropyrimidine 5-FU was synthesized in 1957 and remains the most widely used agent in treating both early and advanced colorectal cancer.

Women receiving 5-FU-based chemotherapy in a five-day bolus schedule experience toxicity more frequently and with greater severity than men. This finding raises the question of whether the recommended initial dose of 5-FU-based chemotherapy should be lower for women.

The largest adjuvant colon cancer trial in the U.S., Intergroup Study 0089, which accrued 3,759 high-risk stage II or III patients for 3.5 years, studied the effect of adding biochemical modulation to 5-FU in the adjuvant setting. This study compared 5-FU plus low-dose leucovorin (LV) versus 5-FU plus high-dose LV versus 5-FU/levamisole versus 5-FU/levamisole plus low-dose LV.

Combining high-risk stage II and III patients, five-year overall survival rates were 64% with 5-FU/levamisole alone, 66% with either high- or low-dose LV added to 5-FU, and 68% with 5-FU plus low-dose LV plus levamisole. Toxicities were related to sex and age. The risks of stomatitis and leukopenia were higher in women than in men and in patients older than 70 years of age compared with younger patients. The incidence of diarrhea was higher in women than in men.

In Intergroup Study 0153, patients who had undergone surgery with curative intent were randomly assigned to receive 5-FU/levamisole, given either by bolus or by continuous infusion. The bolus group also received LV. Overall, infusional 5-FU was as effective as six months’ treatment with bolus 5-FU/LV. The infusional regimen was associated with lower toxicity and with less impairment of quality of life.

A randomized trial of 801 eligible patients compared 12 weeks of infusional 5-FU with a six-month bolus regimen of 5-FU/LV in the adjuvant treatment of colorectal cancer. Five-year overall survival rates were comparable between the two arms (71.5% with bolus 5-FU/LV, 75.7% with infusional 5-FU; \( P = 0.083 \)), as was the five-year relapse-free survival (66.7% for bolus 5-FU/LV, 73.3% for infusional 5-FU; \( P = 0.10 \)).

A retrospective subgroup analysis of patients with rectal cancer showed that the infusional 5-FU regimen significantly reduced the risk of recurrence, compared with the bolus regimen \( (P = 0.0246) \); there was also a trend toward better survival \( (P = 0.0697) \).

The National Surgical Adjuvant Breast and Bowel Project (NSABP) assessed the benefit of the addition of interferon alfa-2a (IFN). Patients with Dukes stage B or C cancer \( (n = 2,176 \text{ patients}) \) were entered into this NSABP C-05 study; they were randomly assigned to receive either 5-FU/LV or 5-FU/LV/IFN.

No statistically significant differences were observed in either disease-free survival (69% with 5-FU/LV, 70% with 5-FU/LV/IFN) or in overall survival (80% with 5-FU/LV, 81% with 5-FU/LV/IFN). The addition of interferon to 5-FU/LV had no effect on overall survival at four years \( (P = 0.41) \). There was also a higher incidence of grade 3 or greater adverse events in the 5-FU/LV/IFN arm than in the 5-FU/LV arm \( (72.1\% \text{ vs. } 61.8\%) \).

The combination of 5-FU, LV, and oxaliplatin (FOLFOX)–based chemotherapy is now the standard of care for patients with advanced colorectal cancer and gastrointestinal cancers. The rationale for this combination was that the folate-dependent enzyme thymidylate synthase (TS) is one of the main targets of 5-FU-based chemotherapy and that the pres...
Irinotecan. Irinotecan HCl (Camptosar, Pfizer) is an antineoplastic agent of the topoisomerase I inhibitor class. The Cancer and Leukemia Group B (CALGB) 89803 trial addressed the addition of irinotecan to the adjuvant treatment (5-FU/LV) of stage III colon cancer (This three-drug combination is known as IFL).38 The study involved 1,264 patients who were randomly assigned to receive a postoperative bolus regimen of 5-FU/LV or bolus IFL.38 IFL was associated with a 2.5% mortality rate and no disease-free survival benefit. It was not recommended for stage III colon cancer patients.

Van Cutsem et al. further addressed the role of irinotecan as adjuvant therapy in colon cancer in the Pan-European Trials in Adjuvant Colorectal Cancer-3 (PETACC-3) study.39 This randomized phase 3 trial compared the following regimens in patients with stage II/III colon cancer:

- Group A1: irinotecan 80 mg/m² plus LV 500 mg/m² plus an infusional 5-FU bolus, followed by 2,000 mg/m² over 24 hours
- Group A2: irinotecan 180 mg/m² plus LV 200 mg/m² plus a 5-FU bolus, followed by 600 mg/m² 5-FU IV over 22 hours

The study included 3,278 patients (stage II/III: 945/2,333 patients). Of these stage III patients, 2,094 received 5-FU/LV with or without irinotecan.

Three-year disease-free survival rates were 62.9% for IFL and 59.9% for 5-FU/LV. Even though the IFL patients experienced slightly more toxicity, the safety profile was acceptable. For the stage III patients, irinotecan did not significantly increase the efficacy of 5-FU/LV; however, in the pooled population of stage II/III patients, IFL did increase the efficacy of 5-FU/LV. Overall survival results are not available.

In the French ACCORD adjuvant trial, 400 patients with high-risk disease (N2 or N1 with obstruction) were assigned to receive 5-FU/LV with or without irinotecan.40 Adjuvant IFL was associated with significantly more grade 3 and 4 neutropenia and diarrhea, compared with 5-FU/LV alone. Furthermore, preliminary results showed no significant improvement in disease-free survival between the two arms. This might be explained in part by the low-dose intensity of IFL in the triple-combination arm, with more dose reductions and cycle delays caused by neutropenia. Thus, three adjuvant trials have not shown a significant disease-free survival advantage when irinotecan was added to either bolus or infusional 5-FU regimens.

Oxaliplatin. Oxaliplatin (Eloxatin, Sanofi-Aventis) is an antineoplastic agent constituted as an organoplatinum complex; the platinum atom is complexed with 1,2-diaminocyclohexane (DACH) and with an oxalate ligand as a “leaving” group (an atom or a group of atoms that is displaced as a stable species).

Used in combination with infusional 5-FU/LV, oxaliplatin is indicated for the adjuvant treatment of stage III colon cancer patients who have undergone complete resection of the primary tumor. The indication is based on an improvement in disease-free survival, with no demonstrated benefit in overall
survival after a median follow-up of four years. When combined with infusional 5-FU/LV, oxaliplatin is indicated for advanced colonic or rectal carcinoma.

In NSABP protocol C-07, the same population of patients (i.e., with stage II and III colon cancer) after stratification was assigned to receive either 5-FU/LV or 5-FU/LV plus oxaliplatin. The study arm receiving oxaliplatin plus a weekly bolus of 5-FU/LV showed significantly improved three-year disease-free survival (76.5%, n = 1,200 patients), compared with the 5-FU/LV arm (71.6%, n = 1,207 patients) (P = 0.004). A higher incidence of neurosensory toxicity and diarrhea was observed with the oxaliplatin-containing regimen. The relative treatment benefit in stage II disease was at least equal to the benefit in stage III colon cancers.

A pooled analysis of four studies with adjuvant chemotherapy indicated that the relative treatment benefit in stage II disease was at least equal to the benefit in stage III colon cancers. The study authors concluded that adjuvant chemotherapy should also be considered the standard of care for stage II colon cancer.

In the Multicenter International Study of Oxaliplatin/5-FU/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC), treatment consisted of infusional 5-FU/LV with or without oxaliplatin (FOLFOX).53-55 (FU2 is the term applied in this study) At four years, an analysis of the entire cohort of 2,246 stage II and III patients indicated that those who had received FOLFOX4 were significantly more likely to be disease-free (75.9% vs. 69.1%, for an absolute difference of 6.8%) (hazard ratio, 0.76; P = 0.0008). This difference was also statistically significant when stage III patients were considered alone (disease-free survival, 69.7% with FOLFOX4 vs. 61% with 5-FU/LV alone). However, the difference was not significant for stage II patients (disease-free survival, 85.1% vs. 81.3%).

In the FOLFOX4 arm, 176 patients (15.7%) died; in the control arm, 194 patients (17.3%) died. The probabilities of surviving to four years were 84% for patients treated with FOLFOX4 and 82.4% for patients treated with 5-FU/LV. These results confirm the benefit of the FOLFOX 4 regimen, which significantly outperformed the 5-FU/LV regimen in survivalability of patients with advanced colorectal cancer. The principal toxicity associated with the addition of oxaliplatin was grade 3 neuropathy, experienced by 137 patients. However, this condition had resolved in more than 60% of cases by one month and in 95% of patients, by one year.

The NSABP Protocol C-07 study and the MOSAIC trial both demonstrated that adding oxaliplatin to either the infusion or the weekly 5-FU/LV bolus significantly improved three-year disease-free survival. Therefore, it has been suggested that adding oxaliplatin to a regimen of 5-FU/LV may improve the adjuvant treatment of colon cancer.

Capecitabine. An alternative strategy to modulating 5-FU–based chemotherapy has been established through the development of oral fluoropyrimidine analogues. Capecitabine (Xeloda, Roche), a fluoropyrimidine carbamate with antineoplastic activity, is an orally administered systemic prodrug of 5’-deoxy-5-fluorouridine, which is converted in the body to 5-FU.

Capecitabine is indicated as a single-agent adjuvant therapy for Dukes stage C (stage III) colon cancer patients who have undergone complete resection of the primary tumor when fluoropyrimidine therapy alone would be preferred. Dukes stage C colon cancer refers to the spreading of the cancer outside the colon to one or more lymph nodes.

The Food and Drug Administration (FDA) approved capecitabine based on its non-inferiority in disease-free survival to a bolus of 5-FU/LV.67 Oxaliplatin for injection was approved in combination with infusional 5-FU/LV for adjuvant stage III colon cancer. Although neither capecitabine nor the combination of oxaliplatin plus 5-FU/LV prolonged overall survival in the adjuvant setting, the combination chemotherapy regimen was associated with improved disease-free survival, compared with 5-FU/LV in stage III colon cancer. Physicians should consider these results when prescribing single-agent capecitabine in the adjuvant treatment of Dukes C colon cancer.

Chemotherapy for Metastasis Capecitabine. Capecitabine (Xeloda) is indicated as first-line treatment of patients with metastatic colorectal carcinoma when fluoropyrimidine therapy alone is preferred. Combination chemotherapy has shown a survival benefit compared with 5-FU/LV alone. A survival benefit better than 5-FU/LV has not been demonstrated with capecitabine monotherapy. The use of capecitabine instead of 5-FU/LV in combinations has not been adequately studied to ensure safety or preservation of the survival advantage.

A multicenter randomized, controlled phase 3 clinical trial in patients with Dukes C colon cancer provided data on capecitabine. A total of 1,207 patients with previously untreated metastasized colon cancer were randomly assigned to receive either oral capecitabine (1,250 mg/m² twice daily on days one to 14 every 21 days; n = 603) or an IV bolus of 5-FU/LV, a Mayo Clinic regimen (n = 604).

Capecitabine was associated with a statistically significant superior response rate (26%), when compared with 5-FU/LV (17%) (P < 0.0002). In a subgroup analysis, capecitabine resulted in consistently superior response rates (P < 0.05), even in patient subgroups with poor prognostic indicators. The median time to response and the duration of response were similar, and the time to progression was equivalent in the two arms (hazard ratio, 0.997; 95% confidence interval [CI] 0.885–1.123; P = 0.95). The median survival rates were 4.6 months with capecitabine and 4.7 months with 5-FU/LV.

A multivariate Cox regression analysis was performed to identify younger age, liver metastases, multiple metastases, and poor Karnofsky Performance Status as independent prognostic indicators for rapid time to progression.

Overall survival was equivalent in the two arms (hazard ratio, 0.95; 95% CI, 0.84–1.06; P = 0.48). Median survival rates were 12.9 months with capecitabine and 12.8 months with 5-FU/LV. Capecitabine resulted in superior response rates, an equivalent time to progression and overall survival, an improved safety profile, and improved convenience, compared with IV 5-FU/LV as a first-line treatment for metastatic colorectal cancer.

When fluoropyrimidine monotherapy is indicated, capecitabine should be considered. It is a suitable replacement for IV 5-FU as the backbone of colorectal cancer therapy.

Bevacizumab. Bevacizumab (BV) (Avastin, Genentech),
combined with IV 5-FU–based chemotherapy, is indicated for the first-line or second-line treatment of patients with metastatic carcinoma of the colon or rectum.\textsuperscript{50} This recombinant humanized monoclonal IgG1 antibody binds to and inhibits the biological activity of human vascular endothelial growth factor (VEGF) assay systems \textit{in vitro} and \textit{in vivo}. BV prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in models of angiogenesis.

In a phase 3 trial, combining bevacizumab plus irinotecan increased survival, compared with irinotecan alone, in the first-line treatment of metastatic colorectal cancer.\textsuperscript{50} Median overall survival rates were 18.3 months with 5-FU/LV/BV (n = 110) and 15.1 months with IFL/placebo (n = 100). Median progression-free survival rates were 8.8 months with 5-FU/LV/BV and 6.8 months with IFL/placebo; overall response rates were 40% with 5-FU/LV/BV and 37% with IFL/placebo; and median response durations were 8.5 months with FU/LV/BV and 7.2 months with IFL/placebo.

Adverse events were consistent with those expected from 5-FU/LV–based or IFL-based regimens, as were modest increases in hypertension and bleeding in the BV arm; these were generally easily managed. The 5-FU/LV/BV regimen seems as effective as IFL and has an acceptable safety profile; it is an active alternative regimen for patients with previously untreated metastatic colorectal cancer.\textsuperscript{51}

Another phase 3 open-label, randomized, three-arm, active-controlled, multicenter clinical trial evaluated BV alone, BV with 5-FU/LV and oxaliplatin (FOLFOX4), and FOLFOX4 alone in the second-line treatment of metastatic colon or rectal carcinoma. Patients had previously received IFL and 5-FU for initial therapy for metastatic disease or as adjuvant therapy. Patients were assigned to receive FOLFOX4 as follows:

- **Day one:** oxaliplatin 85 mg/m\(^2\) and LV 200 mg/m\(^2\) concomitantly IV, then 5-FU 400 mg/m\(^2\) IV bolus, followed by 600 mg/m\(^2\) continuously IV
- **Day two:** LV 200 mg/m\(^2\) IV, then 5-FU 400 mg/m\(^2\) IV bolus, followed by 600 mg/m\(^2\) continuously IV, repeated every two weeks; FOLFOX4 plus BV, or bevacizumab monotherapy.

BV was administered to all patients at a dose of 10 mg/kg every two weeks. Before receiving FOLFOX4 chemotherapy, the patients in the FOLFOX4/BV arm received BV on the first day. Overall survival was significantly longer with BV/FOLFOX4, compared with FOLFOX4 alone. Median overall survival rates were 13 months with BV/FOLFOX4 and 10.8 months with FOLFOX4 alone (hazard ratio, 0.75; 95\% CI, 0.63, 0.89; \(P = 0.001\), stratified log rank test).

Patients receiving BV/FOLFOX4 achieved a significantly longer progression-free survival rate and a higher overall response rate.\textsuperscript{53}

**Cetuximab.** Cetuximab (Erbitux, Bristol-Myers Squibb) is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGF-R).\textsuperscript{52} It is composed of the Fv regions of a murine anti–EGF-R antibody with human IgG1 heavy-chain and kappa light-chain constant regions. Cetuximab is approved as a second-line agent for metastatic colon or rectal cancer; it is also as an IV agent to be given in combination with irinotecan or to be used alone if patients cannot tolerate irinotecan.\textsuperscript{52}

The efficacy and safety of cetuximab, alone or combined with irinotecan, were studied in a randomized, controlled trial of 329 patients and combined with irinotecan in an open-label, single-arm trial of 138 patients. Cetuximab was further evaluated as a single agent in a third clinical trial of 57 patients.\textsuperscript{52} The study also evaluated safety data from 111 patients receiving single-agent cetuximab. All trials studied patients with EGF-R–expressing metastatic colorectal cancer whose disease progressed after receiving an irinotecan-containing regimen. Although positive EGF-R status was required for enrollment in the trials, in practice it is not necessary, because positive EGF-R status does not necessarily correspond to response.

The randomized trial of monotherapy versus combined therapy was conducted in 329 patients who were randomly assigned to receive either cetuximab plus irinotecan (218 patients) or cetuximab monotherapy (111 patients).\textsuperscript{52} In both arms, cetuximab was administered as an initial dose of 400 mg/m\(^2\), followed by 250 mg/m\(^2\) weekly until disease progression or unacceptable toxicity. All patients received a 20-mg test dose on the first day.

In the cetuximab/irinotecan arm, irinotecan was added to cetuximab using the same irinotecan dose and schedule that the patients had not responded to earlier. Acceptable irinotecan schedules were 350 mg/m\(^2\) every three weeks, 180 mg/m\(^2\) every two weeks, or 125 mg/m\(^2\) weekly for four doses every six weeks. An independent radiographic review committee, blinded to the treatment arms, assessed progression with prior irinotecan and the response to the protocol for all patients.

Of the 329 patients, 206 (63\%) were male. Their median age was 59 years (range, 26–84 years), and the majority (98\%) were Caucasian (323 patients). Eighty-eight percent of patients had baseline Karnofsky Performance Status of 80 or above. Fifty-eight percent of patients had colon cancer, and 49\% had rectal cancer. Approximately two-thirds (63\%) of the patients had not responded to irinotecan.

The efficacy of cetuximab plus irinotecan or cetuximab monotherapy was evaluated in all of these patients. Analyses were also performed in two prespecified subpopulations: those with cancer refractory to irinotecan and those not responding to oxaliplatin. The irinotecan-refractory population was defined as randomized patients who had received at least two cycles of irinotecan-based chemotherapy before treatment with cetuximab and with disease progression within 30 days of completion of the last cycle of irinotecan-based chemotherapy.

The irinotecan- and oxaliplatin-failure population was defined as irinotecan-refractory patients who had been treated with, but had not responded to, an oxaliplatin-containing regimen.

Median durations of response in the overall population were 5.7 months in the combination arm and 4.2 months in the monotherapy arm. Compared with patients receiving cetuximab alone, the cetuximab/irinotecan patients experienced a significantly longer median time to disease progression.

Cetuximab plus irinotecan was evaluated in a single-arm, multicenter, open-label clinical trial of 138 patients with
EGF-R–expressing metastatic colorectal cancer. Disease had progressed following an irinotecan-containing regimen using the same dose and schedule of cetuximab as in the randomized trial discussed earlier. Patients received the same irinotecan dose and schedule that they had not responded to previously. Of 138 patients enrolled, 74 patients had documented progression with irinotecan, as determined by an independent review committee. Overall response rates were 15% for the overall population and 12% for the patients not responding to irinotecan. Median durations of response were 6.5 months for the overall population of treated patients (cetuximab/irinotecan) and 6.7 months for the irinotecan-failure population receiving cetuximab/irinotecan.

Cetuximab was also studied as a single agent in a multicenter, open-label, single-arm clinical trial in patients with EGF-R–expressing metastatic colorectal cancer whose disease progressed following an irinotecan-containing regimen. Of 57 patients enrolled, 28 patients had documented disease progression with irinotecan. The overall response rates were 9% for all treated patients (with cetuximab and with cetuximab/irinotecan) and 14% for the irinotecan-failure patients. The median duration of response was 4.2 months for both groups.

Panitumumab. Panitumumab (Vectibix, Amgen) is a human monoclonal antibody that targets the EGF-R, a protein that plays an important role in cancer cell signaling. As an IgG2 monoclonal antibody, panitumumab binds with high affinity to the EGF-R.

Although EGF-R normally regulates the growth of many different cells in the body, it can stimulate cancer cells to grow. In fact, many cancer cells actually require signals mediated by EGF-R for their survival. Residing on the surface of these tumor cells, EGF-R is activated when naturally occurring proteins in the body, such as EGF or transforming growth factor-α (TGF-α), bind to it. This binding changes the shape of EGF-R, which, in turn, triggers internal cellular signals that stimulate tumor cell growth. Panitumumab binds to EGF-R, preventing the natural ligands such as EGF and TGF-α from binding to the receptor and interfering with the signals that would otherwise stimulate growth of the cancer cell and allow it to survive.

Panitumumab is indicated for EGF-R metastatic colorectal cancer with disease progression during or following regimens of fluoropyrimidine, oxaliplatin, and irinotecan. The effectiveness of panitumumab for EGF-R metastatic colorectal carcinoma is based on progression-free survival. No available data have demonstrated an improvement in disease-related symptoms or increased survival with panitumumab.

A multinational, open-label phase 3 study enrolled 463 patients with metastatic colorectal cancer who did not respond to standard chemotherapy, including oxaliplatin and irinotecan. The patients were randomly assigned to receive 6 mg/kg of panitumumab plus best supportive care (n = 231) every two weeks or best supportive care alone (n = 232). An independent, central radiology review board assessed disease progression and tumor shrinkage.

Patients who received panitumumab every two weeks showed a 46% decrease in tumor progression rate, compared with the rate for those receiving best supportive care alone (P < 0.000 000 001). A significantly higher proportion of patients were alive and free of disease progression with panitumumab at all scheduled time points through week 32.

After six months, almost four times as many panitumumab-treated patients were alive and free of disease progression (18%), compared with those receiving best supportive care alone (5%). At week 32, more than twice as many panitumumab patients were alive and free of disease progression (10%), compared with those receiving best supportive care alone (4%). Panitumumab improved disease control, compared with best supportive care alone (36% vs. 10%, respectively), as measured by response rate and stable disease. Objective, independently evaluated response rates were 8% with panitumumab and zero with best supportive care alone. The median duration of response was 17 weeks. Stable disease rates were 28% with panitumumab and 10% with best supportive care alone.

An interim analysis of overall survival was similar for the two groups. The rate (75%) and timing (median, seven weeks) of crossing over from best supportive care alone to receiving panitumumab, as well as the anti-tumor activity observed after the crossover, probably confounded the ability to show a treatment effect on overall survival (hazard ratio, 0.93).

Panitumumab improved progression-free survival and response rate regardless of the measured level or intensity of EGF-R staining. (EGF-R following immunohistochemical [IHC] staining correlates with patient survival. IHC is used to examine EGF-R expression or overexpression in colon tumor tissue.) Improvements in progression-free survival and disease control also occurred regardless of age, sex, location of the primary tumor (colon or rectum), or performance status.

As per the protocol, patients receiving panitumumab did not require premedication or a loading dose, and the incidence of infusion reactions of any severity was low (1%). There were no grade 3 or 4 infusion reactions. More of the panitumumab patients reported skin toxicities, fatigue, abdominal pain, nausea, and diarrhea. Hypomagnesemia was observed in 38% of the panitumumab patients (3% grade 3 and 4). No formation of de novo human anti-human antibody (HAHA) or anti-panitumumab antibody was observed.

Combination Regimens

Adjuvant Chemotherapy in Stage II Disease. Although the benefit of adjuvant chemotherapy has been confirmed in stage III colon cancer, efficacy in patients with stage II disease is not as well established.

The International Multicentre Pooled Analysis of Colon Cancer Trials Investigators (IMPACT) project pooled adjuvant data from trials conducted by Italian, Canadian, French, and U.S. trial researchers among Dukes stage B2 and C colon cancer patients. Patients were randomly assigned to a control arm or to receive 5-FU/LV for six months in four trials and for one year in one trial. The median follow-up period ranged...
from five to 8.5 years.

For the population as a whole, 5-FU/LV was associated with a clear improvement in disease-free survival and overall survival. However, when analyzed according to stage, Dukes B patients show no benefit from treatment in either event-free or overall survival. In contrast, 5-FU/LV appeared to improve both outcomes for stage C patients.

A pooled analysis of stage II patients from four sequential NSABP trials (C-01, C-02, C-03, and C-04) compared adjuvant chemotherapy regimens with each other and with no adjuvant treatment.57 The trial compared the following:

- C-01: semustine (methyl-CCNU)/vincristine (Onconvin)/5-FU (fluorouracil) (MOF) with surgery alone
- C-02: perioperative 5-FU with surgery alone
- C-03: 5-FU/LV with MOF
- C-04: 5-FU/LV versus 5-FU/levamisole versus 5-FU/LV/levamisole

In all four studies, improvement in disease-free and recurrence-free survival was observed in both Dukes B and C patients. The researchers concluded that patients with Dukes B colon cancer benefited from adjuvant chemotherapy and should be offered this option. Whether or not other clinical prognostic factors were present, Dukes B patients improved after chemotherapy.

A panel convened by the American Society of Clinical Oncology, in partnership with the Cancer Care Ontario Program in Evidence-Based Care’s Gastrointestinal Cancer Oncology, in partnership with the Cancer Care Ontario

In terms of prognostic information, it is appropriate to convey that the overall survival rate in stage II disease is 75% to 80% and that any improvement in survival with the addition of chemotherapy is less than 5%. Adjuvant chemotherapy improves survival among patients with stage III colon cancer, but no reliable molecular predictors of outcome have been identified.61

A study was conducted to analyze tumor tissue from 460 patients with stage III and high-risk stage II colon cancer who had received various combinations of adjuvant 5-FU/LV, and 5-FU/levamisole to determine the ability of certain marker chromosomes (18q, 17p, 8p) and cellular levels of p53 and p21<sup>WAF1/CIP1</sup> proteins to predict survival.61 Loss of heterozygosity at 18q was present in 155 of 319 cancers (49%).

High concentrations of microsatellite instability were found in 62 of 298 tumors (21%); 8 of these 62 tumors (13%) had a mutation of the gene for the type II receptor for TGF-β1 in cancers with high concentrations of microsatellite instability.61 However, retention of 18q alleles in microsatellite-stable cancers and mutation of the gene for the type II receptor for TGF-β1 in cancers with high concentrations of microsatellite instability suggest a favorable outcome after adjuvant chemotherapy with 5-FU-based regimens for stage III colon cancer.61

### BIOLOGIC AGENTS IN CLINICAL DEVELOPMENT

Table 1 summarizes some promising agents for treating colorectal cancer.

<table>
<thead>
<tr>
<th>Investigational Drug</th>
<th>Proprietary Name, Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small-molecule tyrosine kinase inhibitors of vascular endothelial growth factor receptor (VEGF-R)</td>
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</tr>
<tr>
<td>PTK 787/ZK 2225B4</td>
<td>Valatinib, Novartis</td>
</tr>
<tr>
<td>SU 5416</td>
<td>Semaxanib, Pharmacia/Sugen</td>
</tr>
<tr>
<td>SU 11248</td>
<td>Sunitinib (Sutent), Pfizer</td>
</tr>
<tr>
<td>SU 6668</td>
<td>Sugen</td>
</tr>
<tr>
<td>Newer inhibitors in early development</td>
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</tr>
<tr>
<td>AAL 993</td>
<td>Novartis</td>
</tr>
<tr>
<td>CEP 7055</td>
<td>Sanofi-Aventis</td>
</tr>
<tr>
<td>CP 547632</td>
<td>OSI</td>
</tr>
<tr>
<td>GW 654652</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>AMG 706</td>
<td>Amgen</td>
</tr>
<tr>
<td>AZD 2171</td>
<td>AstraZeneca</td>
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<tr>
<td>Combined inhibitors of VEGF, tyrosine kinase, and others</td>
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</tr>
<tr>
<td>ZD 6474</td>
<td>Zalzima, AstraZeneca</td>
</tr>
<tr>
<td>AEE 788</td>
<td>Novartis</td>
</tr>
<tr>
<td>BAY 43-9006</td>
<td>Sorafenib (Nexavar), Bayer</td>
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<tr>
<td>Insulin growth factor receptor inhibitors</td>
<td></td>
</tr>
<tr>
<td>NIMC-A12</td>
<td>ImClone Systems</td>
</tr>
<tr>
<td>CP-751871</td>
<td>Pfizer</td>
</tr>
<tr>
<td>AVE 1642</td>
<td>Immunogen/Sanofi-Aventis</td>
</tr>
<tr>
<td>19D2</td>
<td>Schering-Plough</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitors (potential of inhibiting insulin receptors)</td>
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<tr>
<td>NVP-ADW 742</td>
<td>Novartis</td>
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<tr>
<td>NVP-AEW 541</td>
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<tr>
<td>BMS 536924</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>BMS 554417</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>PPP</td>
<td>Karolinska Cancer Institute/Biovitrum</td>
</tr>
<tr>
<td>INSM 18</td>
<td>Insmed</td>
</tr>
<tr>
<td>Src oncogene kinase inhibitors</td>
<td></td>
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<tr>
<td>BMS 354825</td>
<td>Bristol-Myers Squibb</td>
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<tr>
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<td>AZD 0530</td>
<td>AstraZeneca</td>
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<tr>
<td>SKI-606</td>
<td>Wyeth</td>
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</tbody>
</table>

Five-year survival rates for cancer with high levels of microsatellite instability were 74% with a mutated gene for the type II receptor for TGF-β1 and 46% without this mutation (a relative risk of death, 2.90) (95% CI, 1.14–7.35; P = 0.03). Therefore, retention of 18q alleles in microsatellite-stable cancers and mutation of the gene for the type II receptor for TGF-β1 in cancers with high concentrations of microsatellite instability suggest a favorable outcome after adjuvant chemotherapy with 5-FU–based regimens for stage III colon cancer.61
Small-molecule tyrosine kinase inhibitors of VEGF-R. These potent inhibitors of VEGF-R-1, 2, 3 and platelet-derived growth factor receptor (PDGF-R) tyrosine kinase activity have shown significant antitumor activity. Combined inhibitors of VEGF, tyrosine kinase, and others. These agents (e.g., sorafenib and sunitinib) inhibit endothelial cell proliferation by blocking VEGF-induced signaling and inhibit cancer cell growth by blocking EGFR autocrine signaling. The knowledge that tumors depend on new vessel formation for growth beyond a few millimeters has led to a new field of anticancer drug investigation. Angiogenic inhibitors reduce the ability of tumors to develop new blood vessels, slowing or stopping its growth, not necessarily by targeting tumor cells but by interacting with tumor-related endothelial cells.

VEGF is one of the most important angiogenic factors in patients with colorectal cancer, and its circulating level is associated with the aggressiveness, stage, and prognosis. Thus, drugs targeting either VEGF or its cell surface receptor have attracted major interest.

SU-5416, like other tyrosine kinase inhibitors, is a potent and selective synthetic inhibitor of the Flik/1/kdr VEGF receptor tyrosine kinase. It targets the VEGF pathway, and in vivo and in vitro studies have highlighted its antiangiogenic potential. It inhibits VEGF-dependent mitogenesis of human endothelial cells but does not affect the growth of various tumor cells in vitro, confirming the VEGF receptor (VEGF-R) on endothelial cells as its main target.

Insulin growth factor receptor (IGF-1-R) inhibitors. Increased expression of type I IGF-1-R is associated with cancer, and inhibitors of IGF-1-R are now a target of intensive research. The IGF ligand-receptor system is important in multiple mechanisms that mediate human colon cancer growth, including regulation of VEGF and angiogenesis.

Src oncogene kinase inhibitors. Elevated levels of Src kinase expression are found in human epithelial cancers. Most notably in colon cancer, elevated Src expression correlates with malignant potential and is associated with metastatic disease. Src expression is often elevated in epithelial tumors (colon, breast, pancreas, lung, ovarian), compared with the adjacent normal tissues. In colon cancer, increased Src expression is linked to malignant potential, with increases seen in premalignant lesions and adenomas but with highest levels seen in malignant polyps.

CONCLUSION

Colorectal cancer is the second most common cause of death from cancer in much of the developed world. Intense research has led to the introduction of three novel cytotoxic agents (capcitabine, irinotecan, oxaliplatin) and the recent approval of three antibodies (bevacizumab, cetuximab, panitumumab). Several novel biologic agents and targets are also in phase 2 clinical studies, and their contribution to future therapy for colorectal cancer remains to be seen.

Colorectal cancer has become an excellent tumor model for evaluating new therapeutic strategies. Understanding how this cancer develops and grows allows a tailored approach to all stages of treatment: prevention, adjuvant therapy, and therapy for advanced disease. Thus, specific molecular processes have been targeted for therapeutic intervention, including growth factor receptors, proliferation signaling, cell cycling, apoptosis, angiogenesis, and the immune system.

Survival rates for patients with metastatic colorectal cancer have nearly doubled. With the incorporation of biologic agents that target angiogenesis (bevacizumab) and tumor growth pathways (cetuximab), researchers have noted additional improvements in these patients. The benefit of these newer drugs is also realized in the adjuvant setting (e.g., adding oxaliplatin to 5-FU/LV, which has led to improved three-year disease-free survival). Future adjuvant studies are needed to determine whether adding new biologic agents to cytotoxic chemotherapy regimens will result in increased overall survival.

REFERENCES


