Has Real Progress Been Made in Chemotherapy for Colon Cancer?

The introduction of capecitabine, irinotecan, oxaliplatin, and the anti-angiogenesis agent, bevacizumab, has significantly increased the response rate, the time to progression, the median survival time, and the overall cure rate for patients with colorectal cancer. Capecitabine, a pill, is easier to administer, less expensive, and more effective than the prior best treatment regimen, infusion 5-FU/Leucovorin. Its major side effect, hand-foot syndrome, may be minimized and its therapeutic benefit increased by the administration of the COX-2 inhibitor, Celebrex. Continuing studies suggest that capecitabine/oxaliplatin/bevacizumab may prove to be the most effective first-line treatment for both advanced colorectal cancer and as adjuvant therapy for patients with completely resected lesions who have a high risk of systemic recurrence. Targeted therapy against growth promoting molecules may supplement or eventually even replace chemotherapy regimens once such targets have been identified in colorectal cancer tissue.

You live in a primitive, iron-age culture on an island. Your most sophisticated weapon is a spear; your means of transport, a canoe, and your best defense is the sea that surrounds you.

Several miles away, on a second island, lives your enemy, similar to you in all respects except, somehow, the enemy has an armed and fueled jet fighter plane. A canoe and a spear is no match for a fighter plane...unless...You row your canoe to the enemy island under cover of darkness; use your spear to deflate the tires on the plane, and return to your island knowing that since the plane can no longer take off, the imminent threat to you has been eliminated. (Personal Communication—Dr. Marc E. Lippman) The clinical battle to control colorectal cancer, similar to the battle between the spear and the fighter plane, is focused on the search for all vulnerabilities within the growing tumor, which might be exploited for the benefit of the affected patient.

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The newest developments in the use of systemic therapy for the management of colorectal cancer center around the introduction of three chemotherapeutic agents: capecitabine, irinotecan, and oxaliplatin, and, instead of the spear, bevacizumab (Avastin), a monoclonal antibody against Vascular Endothelial Growth Factor (VEGF) activity. These agents used alone and in combination have improved response rates and survival times of affected patients. Until we have a better understanding of what causes this form of cancer so that the cause can be eliminated and the condition prevented, the small but significant improvements afforded by these new agents in the treatment of colorectal cancer should be understood, employed and studied to allow for continuing enhanced results.

Colorectal cancer is the second most common visceral malignancy, after lung cancer, diagnosed in the United States. The total number of new cases has remained reasonably constant between 1990 (155,000) (1) and the present (147,5000) (2). In 1990, 57,158 people died of colorectal cancer. In 2003, 57,100 are projected to have died from this disease. In the United States, the lifetime risk of developing a colorectal cancer is roughly one in 20 (3).

Reported relative survival rates for patients diagnosed with colorectal cancer are dependent largely on the degree of spread encountered at the time of diagnosis. Localized cancers, which have not invaded the serosa and have not spread to involve regional lymph nodes, are estimated to have a survival rate of approximately 90%. Once lymph node involvement is encountered the five-year relative survival rate falls to 65%. Distant spread, beyond the regional lymph nodes, is associated with a relative five-year survival rate of 10% (2).

Sixty percent of patients with colorectal cancer will have liver metastases sometime during the course of their disease, and 15 percent will have liver metastases at diagnosis (4).

For these patients, systemic chemotherapy, which can shrink liver metastases to a level allowing for attempted curative surgical resection, can result in a five-year survival rate of up to 37% (5).

5-Flourouracil (5-FU), a metabolic inhibitor of nucleic acid synthesis, has been the backbone of colorectal cancer chemotherapy since before medical oncology was recognized as a subspecialty of internal medicine. Although initially administered in intermittent bolus doses, randomized studies have demonstrated a higher tumor response rate (22% v. 14%) and a slight (12%) improvement in overall survival when continuous infusion 5-FU was compared to bolus 5-FU in a meta-analysis of over 1200 patients from six different trials (6).

The addition of calcium leucovorin to 5FU has further improved the therapeutic index of 5-FU chemotherapy in the management of metastatic colorectal cancer (7), and, until recently, this combination was accepted as standard therapy in both the metastatic setting and in the adjuvant treatment of Duke’s C colorectal cancer (i.e. Involved regional lymph nodes) (8,9).

5-FU is not orally available since it is not absorbed well in the gastrointestinal tract. Capecitabine (Xeloda), an oral fluoropyrimidine which is selectively converted to 5FU in tumor cells, and which closely mimics the long-term, low-dose exposure effects of continuous IV 5-FU, is absorbed. It passes through the gastrointestinal epithelium and is metabolized in the liver. It is then converted to its active form by the enzyme thymidine phosphorylase, which is found in higher concentrations in tumors than in normal tissue (10).

Studies have demonstrated that capecitabine is either more active (22% vs. 13% response rate) (11) or as active as 5-FU/Leucovorin (5-FU/LV) in the treatment of advanced colorectal cancer, with the only major toxicity being hand-foot syndrome. (12,13) The incidence and severity of hand-foot syndrome may be prevented and/or reduced by the administration of pyridoxine (vitamin B6) or the cylooxygenase 2 (COX-2) inhibitor celecoxib (Celebrex). COX-2 has been found to be overexpressed in premalignant, malignant, and metastatic cancers. It is unregulated in 85% to 90% of colorectal carcinomas (14) and the level of COX-2 overexpression has been shown to correlate with invasiveness, prognosis and survival (15).

COX-2 promotes tumor-specific angiogenesis, inhibits apoptosis, and induces Vascular Endothelial Growth Factor (VEGF). Several mechanisms by which COX-2 inhibition exerts anti-cancer effects have been suggested and include inhibition of angiogenesis,
reduction of cell adhesion molecules, and inhibition of apoptosis. Randomized trials have demonstrated that celecoxib (Celebrex) inhibits the growth of adenomatous polyps in patients at high risk with familial adenomatous polyposis (16).

Results of a small and retrospective study in patients with advanced colorectal cancer suggest that treatment with capecitabine plus celecoxib in comparison with capecitabine alone reduces the incidence of hand-foot syndrome and may also improve tumor response (17).

A recent report suggests that treatment with oral capecitabine, in addition to being less toxic and, possibly, more effective, is also less expensive than intravenous 5-FU/leucovorin treatment (18).

Capecitabine compared to bolus 5-FU/LV as adjuvant therapy for colon cancer, was associated with a significant reduction in stomatitis, diarrhea, nausea/vomiting, alopecia and neutropenia. Hand-foot syndrome was more common in the capecitabine arm. The efficacy results should be available in 2004 (19).

Irinotecan is a member of the topoisomerase-1 (TOP-1) inhibitor class of anti-neoplastic compounds. In humans, TOP-1 expression increases during cell proliferation. TOP-1 activity is higher in colorectal tumors than in normal colorectal tissue—which may enhance the selectivity of irinotecan for malignant versus normal tissue. Irinotecan added to 5FU/LV has demonstrated higher activity against colorectal cancer and improved overall survival when compared to 5FU/LV alone (20). A second study in patients with metastatic colorectal cancer demonstrated that the combination of 5-FU/LV plus irinotecan was superior to either 5-FU/LV alone or irinotecan alone(21). In these studies, response rates were 39% for the individual drugs and 49% for the combination. Median overall survivals were 14.8 and 17.4 months respectively. The irinotecan/5-FU/LV (IFL) regimen of Salz used bolus 5-FU, while the Douillard regimen (FOLFIRI) employed both bolus and infusional 5-FU.

When capecitabine was substituted for 5-FU/LV in combination with irinotecan in the treatment of advanced colorectal cancer, an overall response rate of 71% was reported by Cassata et al (22).

A subsequent report by Borner et al, presenting the effect of capecitabine plus irinotecan in the treatment of advanced colorectal cancer, noted a response rate of 43% together with a median time to progression of 9.3 months (23).

Oxaliplatin, the only platinum derivative with in vivo activity against colorectal cancer, has been added to infusion 5-FU/LV (FOLFOX4) and compared to bolus 5-FU/LV plus irinotecan (IFL) in the treatment of advanced colorectal cancer. The response rates were 40% for the oxaliplatin combination (FOLFOX4) and 30% for the irinotecan-containing regimen (IFL), with a significant p value of .02. Time to progression was 8.8 months (FOLFOX4) vs. 6.9 months (IFL) with a p value of .004. Median survival was 19.1 months for FOLFOX4 and 14.8 months IFL (24).

Capecitabine added to oxaliplatin (XELOX) and used in the treatment of advanced colorectal cancer has been reported to show a response rate of over 50% (25). Oxaliplatin plus infusional 5-FU/LV (FOLFOX4) has recently been shown to be slightly more effective than infusional 5-FU/LV in the adjuvant treatment of stage III (regional node involvement) colorectal cancer with 3-year disease-free survivals of 78% vs. 73% respectively (26,27). The benefit of adjuvant therapy in the management of stage II colorectal cancer remains undecided.

One of the major cellular changes associated with solid tumor development and progression is overexpression of protein kinases, such as the epidermal growth factor receptor (EGFR). Ligands for this receptor (substances which bind to it) have been shown to induce production of vascular endothelial growth factor (VEGF), which in turn stimulates angiogenesis (the process by which tumors establish a blood supply which is required for tumor growth and spread) (28).

Methods to target the EGFR receptor include monoclonal antibodies that block ligand binding, and small molecules that inhibit cytoplasmic tyrosine kinase activity directly. Epidermal growth factor receptor antagonists have been shown to inhibit cell cycle progression, decrease angiogenesis, decrease rates of metastases, and increase sensitivity to chemotherapy-induced tumor cell death. Several observations make the EGFR a rational therapeutic target for colorectal cancer. Overexpression of the EGFR occurs in 60%-75% of colorectal carcinomas (29), and has been correlated with a poor prognosis, disease progression, and
metastatic potential (30). Vascular endothelial growth factor is the predominant angiogenic factor in human colorectal cancer and its overexpression has been shown to correlate with advanced stage and inferior prognosis (31).

A recombinant humanized monoclonal antibody against VEGF (i.e. bevacizumab = Avastin) has been developed and is currently in clinical trials. This antibody inhibits the binding of VEGF to its endothelial cell receptors and has been shown to inhibit tumor-associated angiogenesis in animal models. A recently reported Eastern Cooperative Oncology Group trial compared bolus 5-FU/LV, irinotecan (IFL) with the same regimen plus bevacizumab in patients with previously untreated metastatic colorectal cancer. The overall response rate was 35% with IFL and 45% with IFL/bevacizumab (P = 0.0029). The median progression-free survival was prolonged from 6.2 to 10.6 months by the addition of bevacizumab (P < 0.00001), and the overall survival was extended from 15.6 to 20.3 months (P = 0.00003) (32).

A concurrent study evaluating the possible benefit of adding bevacizumab to the infusion/5-FU/LV/Oxaliplatin regimen (FOLFOX4) in patients with advanced colorectal cancer has found only mildly increased toxicity by the addition of bevacizumab (3% serious bleeding events and 7% incidence of hypertension). Since FOLFOX4 has already been shown to be more effective than bolus 5-FU/LV/irinotecan (IFL), the therapeutic results of this trial are awaited with interest (33).

The words breakthrough and exciting are overused by medical oncologists and by lay journalists covering cancer treatment stories. We are, nevertheless, entering a period of targeted therapy, which will probably revolutionize the field. Until recently, gastrointestinal stromal tumors (GIST) were unresponsive to clinical modalities and generally fatal. As a result of the identification of a molecular abnormality(c-kit gain-of-function mutation identified in a transmembrane receptor tyrosine kinase) a specific inhibitor of this kinase activator has been developed. This inhibitor (imatinib mesylate or Gleevec) is a pill capable of reproducibly inducing complete remissions in the majority of patients suffering from GIST (34–36). Until a comparable targeted therapy for colorectal cancer is developed, small incremental benefits in response rates, times to progression, median survival times, and even overall cure rates when unresectable metastases are converted to resectable lesions by the use of the evolving new therapies described in this review, can reasonably be anticipated. In the not too distant future, oral capecitabine (Xeloda) plus Celebrex plus oxaliplatin plus bevacizumab will almost certainly be tested for efficacy against measurable, unresectable tumor, and, if the therapeutic benefit is similar to or better than that of IFL/bevacizumab or FOLFOX4/bevacizumab, this regimen could become the next standard of care in the treatment of both advanced colorectal cancer and as adjuvant therapy following surgical resection.

References

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ship between cyclooxygenase-2 expression and colorectal cancer. JAMA, 1999;282:1254-1257.


