The Role of Chemotherapy in Colon Cancer

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Chemotherapy is effective in the treatment of colon cancer when used both as adjuvant therapy and for metastatic disease. It has also been shown to improve survival. Novel therapies are currently being evaluated in clinical trials. To continue our progress, it is important that clinical trials be offered to patients undergoing treatment for colon cancer.

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Colorectal carcinoma is a major public health problem in the United States and in most developed countries. It is the second leading cause of death from cancer in the US and Europe (1). Fortunately, the incidence and mortality were observed to be declining between 1986 and 1996, and this trend continues. Several factors, including improved diet, physical activity, and decreased smoking rates, are being credited for this decrease (2).

Chemotherapy has improved survival in colon cancer patients both with resectable and unresectable disease. Since three-quarters of patients diagnosed in the US are surgically resectable, an effort to decrease relapse rates while improving overall survival with adjuvant treatment has been an important step in the evolution of the treatment of colon cancer. Drugs that first proved their efficacy in the metastatic setting have been evaluated in the adjuvant setting, and several novel drugs are under evaluation both as adjuvant therapy and for metastatic disease.

Chemotherapy in Metastatic Colon Cancer

Chemotherapy has traditionally played a palliative role in metastatic disease; however, newer combinations have also been shown to prolong survival. Surgery should still be considered for patients with isolated recurrence at the site of anastomosis or isolated resectable liver metastases. Elderly patients with good performance status tolerate palliative chemotherapy as well as younger patients and have similar benefits in quality of life and survival with no significant difference in toxicity (3).

5 Fluorouracil

The single most important drug in colon cancer treatment is 5-fluorouracil (5-FU). It is administered intravenously because of erratic bioavailability when given orally (due to varying levels of dihydropyrimidine dehydrogenase [DPD] in the gastrointestinal tract). Response rates range from 15%-20%. Efforts to enhance the efficacy of 5-FU led to the use of leucovorin as a biochemical modulator. 5-FU is converted to fluorodeoxyuridylate, which binds to and inhibits thymidylate synthase in the presence of L-5,10 methylene tetrahydrofolate. The addition of leucovorin was shown to result in higher response rates than 5-FU alone, although with greater incidence of toxic effects (mucositis and diarrhea) (4,5). When protracted 5-FU infusion was compared with a bolus method of delivery, the toxicity profiles for the two regimens differed: increased mucositis and palmar-plantar erythrodysesthesia (hand-

foot syndrome) for the protracted infusion regimen and increased myelosuppression and diarrhea for the 5-FU bolus regimen (6,7). The erratic oral bioavailability of 5-FU was overcome by the development of prodrugs that are absorbed enterally and then converted to 5-FU or by the coadminstration of DPD inhibitors. These offer ease of administration and have been evaluated in colon cancer and other tumor types (8,9).

Oral Fluoropyrimidines

Capecitabine is an oral fluoropyrimidine that is absorbed in the stomach, metabolized in the liver, and activated at the tumor site by thymidine phosphorylase to 5-FU. It has at least an equivalent, if not better response rate when compared with bolus 5-FU + leucovorin, but with no improvement in survival (10,11). Toxicity includes diarrhea and hand-foot syndrome. Currently, capecitabine is approved in the US and Europe as first-line therapy for advanced colon cancer.

UFT (a combination of uracil, a DPD inhibitor; 5-FU; and tegafur, a 5-FU prodrug), another oral fluoropyrimidine in combination with leucovorin, has been compared with 5-FU + leucovorin in phase III trials, but for technical reasons failed to show equivalence and was not approved by the Food and Drug Administration (12). The Eastern Cooperative Oncology Group (ECOG) is conducting a phase II trial using UFT + oral leucovorin in elderly patients with advanced colon cancer.

Irinotecan

Irinotecan, a topoisomerase I inhibitor developed in Japan, has clinical activity in metastatic colorectal cancer. A European and an American phase III trial studied the addition of irinotecan to 5-FU + leucovorin. The results of these trials were consistent and resulted in improved response rates from 35% to 40% with a median time of disease-free progression of 7 months, making this combination the new standard of care in the treatment of metastatic colon cancer (13,14). Its primary toxicities are diarrhea and leukopenia, which may be severe or life threatening and, therefore, appropriate care must be taken to ensure patient safety with this combination.

Oxalipatin

Oxaliplatin is a diaminocyclohexane (DACH) platinum compound active in patients with colon cancer previously treated with 5-FU. A recent French phase III trial studied the combination of chronomodulated 5-FU + leucovorin with or without oxaliplatin as first-line therapy for metastatic colorectal cancer. The study showed that oxaliplatin improved response rates significantly (53% vs. 16% for 5-FU + leucovorin). Progression-free survival was also improved (8.7 months vs. 6.1 months); however, median survival was not (15). Giacchetti et al confirmed these findings by showing significant improvement in response rates and progression-free survival, but, again, no improvement in overall survival (16). Oxaliplatin has an acceptable toxicity profile, but, due to the failure to demonstrate improvement in overall survival, is not yet approved in the US. Clinical trials are ongoing.

Floxuridine

Implantable infusion pumps allow chemotherapeutic agents to be delivered directly into the hepatic artery to treat metastatic disease confined to the liver. This method permits prolonged drug exposure, at higher concentration to the tumor cells. Floxuridine (FUDR) has been delivered in this manner for hepatic intra-arterial chemotherapy. Two meta-analyses summarized the data of randomized trials comparing regional FUDR therapy with systemic 5-FU (17,18). The results suggested higher response rates and possible increased survival in the regional therapy group. In two randomized trials with patients who had surgical resection of hepatic metastases and received intra-arterial FUDR versus observation or systemic chemotherapy alone, hepatic recurrences decreased, and 2-year survival improved (19,20). The downsides were expense and toxicity, which included gastroduodenal ulcers, hepatitis, and sclerosing cholangitis. The Cancer And Leukemia Group B (CALGB) is conducting a prospective comparison of systemic 5-FU + leucovorin and regional hepatic artery infusion with FUDR, leucovorin, and dexamethasone for patients with metastatic unresectable disease confined to the liver.

Raltitrexed

Raltitrexed is a potent selective inhibitor of thymidine synthetase that has the ability to stay in cells for long periods of time, making for convenient dose scheduling. It is currently approved in Canada, Europe, and South America. However, a phase III American trial comparing single agent raltitrexed with 5-FU + leucovorin showed a significant difference in overall survival favoring the 5-FU + leucovorin regimen (21).

Interferons

Interferons (IF) -alpha, -beta, and -gamma have been shown to enhance the activity of 5-FU both in vitro and in vivo by different mechanisms, but this has not translated into improved clinical outcomes (22).

Adjuvant Chemotherapy in Colon Cancer

In 1988, the first definitive evidence that adjuvant chemotherapy improved disease-free survival and overall survival in completely resected colon cancer was reported by the National Surgical Adjuvant Breast and Bowel Project (NSABP) (23) and confirmed the subsequent year by the North Central Cancer Treatment

Group (NCCTG) (24). However, the data suggested that the benefit was limited to patients with node-positive disease. In the NCCTG study, levamisole, an antihelmintic agent with nonspecific immunostimulating properties, was found to be effective in combination with 5-FU. An intergroup study published in 1995 confirmed a 40% reduction in recurrence and a 33% improvement in overall survival in patients treated with 5-FU + levamisole as compared with levamisole or surgery alone (25,26). Patients started treatment within 3-5 weeks of surgery and continued treatment for 12 months (27).

The commonly used regimens today are the Roswell Park Regimen of weekly 5-FU and high-dose leucovorin and the Mayo Regimen of 5-FU and low-dose leucovorin given daily for 5 days every 4 weeks (28,29). Both have equivalent efficacy, but the high-dose leucovorin regimen is associated with higher toxicity (30). The results of the intergroup trial INT 0089 were released in 1998 and involved 3759 patients, 80% with stage III and 20% with stage II colon cancer (29). The efficacy was equal for each of the regimens evaluated: 5-FU and levamisole for 12 months, 5-FU + levamisole + low-dose leucovorin for 6 months, monthly 5-FU + leucovorin for 6 months, and weekly 5-FU + high-dose leucovorin for 6 months. Adjuvant therapy with 5-FU + leucovorin for 6 months is now widely preferred because of the shorter duration and better toxicity profile. There is also evidence that both elderly and younger patients have a similar benefit from this therapy without a significant increase in toxic effects (3,31).

The role of adjuvant treatment for stage II colon cancer has remained controversial. A large intergroup trial reported no benefit from adjuvant therapy (32). A later report using data from four NSABP trials of adjuvant therapy showed a 31% reduction in recurrence in stage II disease (33). A meta-analysis published in 1999 pooled patients from five international randomized trials using 5-FU + leucovorin compared with observation. This analysis did not support the routine use of this therapy in all patients with Dukes' B2 colon cancer (34), and the role of chemotherapy in this group is yet to be defined. High-risk patients with stage II colon cancer may be candidates for adjuvant therapy if they have risk factors based on tumor site, depth of invasion, and emergency presentation. A recent German study demonstrated significantly lower disease-related survival and a higher risk of distant metastases in this group of patients (35).

Novel Therapies

Several molecular-targeted agents are being investigated for metastatic colon cancer. The epidermal growth factor receptor (EGFR) has a domain for binding ligands resulting in activation of the enzyme tyrosine kinase and other events involved in signal transduction in cancer cells. Monoclonal antibodies directed against EGFR, such as C225, have been studied in colon cancer with demonstrable activity (36). Multiple tyrosine kinase inhibitors are also under evaluation. The vascular endothelial growth factor (VEGF) inhibitor SU5416 and rhuMAb-VEGF are other molecular-targeted therapies undergoing clinical trials.

Several trials of novel therapies are also being conducted in the adjuvant setting:

- A placebo controlled randomized trial by a German group showed that patients with stage III colon cancer treated with the monoclonal antibody 17-1A had a 23% reduction in recurrence and a 32% reduction in mortality (37,38).
- A US phase III trial comparing standard therapy with 5-FU + leucovorin or 5-FU + levamisole with or without the monoclonal antibody 17-1A has recently completed patient accrual, and results are highly anticipated.
- Another phase III trial investigating monoclonal antibody 17-1A versus observation for stage II colon cancer is being conducted.
- Based on the results of improved response rates with the triplet combination of irinotecan + 5-FU + leucovorin in metastatic colon cancer, an intergroup trial by CALGB is underway comparing standard weekly 5-FU + leucovorin with or without irinotecan.
- A trial of adjuvant therapy using UFT compared with standard chemotherapy by the NSABP was completed in 1999 and results are awaited.
- Capecitabine is also being evaluated in trials as adjuvant therapy.
- An NSABP trial comparing 5-FU + leucovorin with or without oxaliplatin as adjuvant treatment is currently open.

Conclusion

A fair amount of progress has been made since chemotherapy was first used to palliate metastatic colon cancer. Today, it is well recognized that there is a survival benefit when chemotherapy is used in the metastatic setting. Elderly patients with good performance status also benefit from treatment. Adjuvant 5-FU-based chemotherapy is the standard of care in Duke's C disease and may also be of benefit in high-risk B2 disease. Clinical trials using novel therapies offer patients other treatment options. It is important that these trials be offered to patients undergoing treatment for colon cancer both in the adjuvant and in the metastatic setting.

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