Chemotherapy of colorectal cancer

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SUMMARY

Approximately 75% of all patients with colorectal carcinoma will present at a stage when all gross carcinoma can be surgically resected. Despite the high resectability rate, half of all patients with colorectal adenocarcinoma die from metastatic disease, primarily because of residual disease that is not apparent at the time of surgery. These patients are candidates for adjuvant local or systemic therapies. Systmemic chemotherapy is the treatment of choice as well as for patients with recurrent or metastatic disease.

1. SYSTEMIC ADJUVANT THERAPY OF COLONIC CANCER

Until recently, there was no convincing evidence that postoperative systemic adjuvant treatment was effective in decreasing the risk of tumor relapse and death in patients undergoing surgery for primary colonic cancer. However mature data from two prospectively randomized clinical trials has clearly established that 5-fluorouracil (5FU) combined with levamizole can substantially improve relapse free and overall survival in patients with node positive stage III (C) colonic cancer. Emerging data suggests that 5Fu combined with leukovorin (LV) may also be an effective systemic surgical adjuvant therapy, although follow-up of these clinical trials is not currently sufficient to accurately assess impact on 5 year survival.

a. Levamisole plus 5FU

Levamisole, an anthelmintic agent with non-specific immunostimulating properties, plus 5FU, was the first adjuvant regimen to demonstrate a decrease in recurrence rate and increases in disease free and overall survival in patients with stage III colon cancer. These beneficial results, reported in a randomized, controlled study, have been updated at 7 years and demonstrate the effectiveness of the regimen in stage III colon cancer[1]. A total of 929 patients with stage III colon cancer were randomized to receive either surgery alone versus levamisole alone, or 5Fu and levamisole in combination. The 5Fu and levamisole combination reduced the relapse rate by 41% and the overall cancer mortality by 33% Levamisole alone was not significantly different from the surgery alone control crown.

Adjuvant therapy for patients with stage III colon carcinoma, using 5FU plus levamisole should be initiated 3-5 weeks after surgery. The suggested dosage of 5fU is 450 mg/m2 by rapid injection, daily for 5 days, then weekly for 48 weeks, starting on day 28 following surgery. Levamisole, 50 mg orally 3 times daily for 3 days every 2 weeks for 1 year, is recommended in this adjuvant schedule. Although well tolerated by patients, levamisole has been shown to be associated with progressive multifocal leukoencephalopathy in rare patients. This regimen has been largely replaced by the combination of 5FU and leukovorin.

b. 5FU plus leukovorin (LV)

Several studies have suggested the benefits of 5FU plus leukovorin calcium (folinic acid) in the adjuvant treatment of colon carcinoma. The International Multicenter Pooled Analysis of Colon Cancer Trials (IMPACT)[2] pooled analyses of three trials conducted in Canada, France and Italy that included 1493 eligible patients with Dukes' B and C colon cancer, randomized to 5FU and LV or surgery alone.

Data revealed 3-year recurrence-free and overall survival rates with statistically significant improvement with

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adjuvant chemotherapy versus surgery alone, with reduction in failure events by 35% ($p<0.0001$) and overall mortality reduction of 22% ($p=0.029$).

Currently a growing number of trials suggest that 5FU and leukovorin is equivalent or possibly better than 5FU and levamisole in combination. Treatment with adjuvant chemotherapy with 5FU and LV for longer than six cycles does not appear to be necessary.

A 2151-patient National Surgical Adjuvant Breast and Bowel Project (NSABP) trial demonstrated that weekly 5FU/LV is superior or equal to 5FU plus levamisole containing arm. Increased benefit was found with six cycles of weekly 5FU-LV for 6 consecutive weeks of every 8 weeks versus 5FU and levamisole, or 5FU, LV and levamisole combination. Significantly prolonged DFS, 65% versus 60% ($p=0.04$) and prolonged overall survival 74% versus 70% ($p=0.07$) for the LV were found containing arms. No difference was observed when levamisole was added to 5FU and LV[3].

Acceptable adjuvant regimens of 5FU plus LV for colon cancer include:

- a "low dose LV" regimen, consisting of LV (20 mg/m2) immediately followed by 5FU (425 mg/m2), both given by rapid IV injections daily for 5 consecutive days, with courses repeated every 4 weeks to 6 months
- a "high dose weekly LV" regimen, consisting of 5FU (500 mg/m2) by rapid IV injection given at 1 hour during a 2 hour infusion of LV (500 mg/m2) weekly for 6 weeks, with courses repeated every 8 weeks for 4 cycles

Despite 75% 5 year survival with surgery alone, some stage II patients have a higher risk of relapse, with outcomes similar to those of node positive patients. Adjuvant chemotherapy provides up to 33% overall survival advantage, resulting in an overall treatment benefit of roughly 8%. The NSABP summary of protocols using various treatments reported a 30% risk reduction[4], whereas a Canadian European consortium noted no significant benefit.

2. ADJUVANT CHEMOTHERAPY FOR RECTAL CANCER

Patients with primary sites in the rectum were not distinguished from patients with more proximal adenocarcinomas in the late 1960s – early 1970s generation of adjuvant single-agent chemotherapy trials that failed to demonstrate consistent evidence of benefit. Subsequently, however, recognition of the higher risk of local recurrence led to randomized trials specific for rectal cancer patients, usually incorporating a combined modality approach to address both the characteristics, local and distant pattern of failures[5-9].

Clinical trials of surgical adjuvant treatment indicate that postoperative radiation therapy with concurrent chemotherapy (chemoradiation) is superior to postoperative radiation alone or surgery alone. Postoperative chemoradiation is a standard of care for patients with stage II or III rectal cancer based largely in the findings of the North Central Cancer Treatment Group (NGCTG)[10] and Gastrointestinal Tumor Study Group (GITSG) trials.[11,12]

Acceptable adjuvant combined modality regimens for rectal cancer is considered:

- 5FU by intravenous bolus injection at 500 mg/m2 on days 1 – 5 and 36 – 40, followed by
- radiation therapy in 180 cGy fractions given over 5 weeks starting day 64, to a total dose of 4500 – 5400 cGy in association with 5FU, 225 mg/m2/day by ambulatory infusion pump during the entire 5 week period of radiation therapy, followed by
- intravenous bolus of 5FU, 450 mg/m2/day given daily for 5 days on days 134 – 138 and days 169 – 173, for a total treatment period of 6 months.

3. TREATMENT OF ADVANCED COLON CANCER

The development of chemotherapy for the treatment of colorectal cancer has become a very active field and has paralleled the development of 5FU as an effective antineoplastic agent.

After decades of 5FU-based chemotherapy and of little clinical gain, the introduction of new agents has significantly changed the way this cancer is treated. Although 5FU remains the base of most regimen, the new agents irinotecan (CPT 11) and oxaliplatin (Eloxatin) are rapidly becoming an important part of first line treatment of colorectal cancer. The development of newer agents, such as the molecular–targeted agents, promise that progress will continue in the chemotherapy of this disease.

a. 5FU – based chemotherapy

5FU, synthesized by Heidelberg in 1957, remains an important agent in the treatment of advanced color cancer.

Single arm phase II studies of 5FU-based chemotherapy regimens in advanced colorectal cancer have reported a response rate ranging from 0 to 70%, but most larger studies have observed objective response rates of 20% to 25%. Median survival times of 8 to 12 months are quite common. Considerable enthusiasm was generated for the addition of semustine to 5FU following the report from Mayo Clinic of a small randomized comparison of semustine, vincristine and 5FU (MOF) versus 5FU alone in patients with metastatic colorectal cancer[13]. The objective response rate for MOF was more than twice that for 5FU (43 vs 19%), but no significant survival advantage was observed. Subsequent attempts to confirm this superiority have produced variable results, and response rates for MOF or MF (semustine and 5FU) regimen have ranged from 4 to 40%.[14-17] Other studies attempting to substitute Mitomycin C for the nitrosourea or to employ multiple nitrosoureas, such as MOF plus streptozotocin, have not produced greater objective tumor regression than expected from 5FU alone.[18-20]

More recently, the addition of cisplatin to 5FU has been evaluated based, on preclinical studies demonstrating synergy between these agents. While initial phase II studies demonstrated response rates of 30-40%, several randomized trials failed to demonstrate any advantage of the combination over 5FU alone in response rate or survival[21-22]. In view of the increased toxicity that results from the addition of cisplatin, these regimens cannot be recommended for routine clinical use. Because there are a limited number of effective agents for treatment of colorectal cancer, most recent studies have focused on biochemical modulation of 5FU and on alterations of the route and schedule of 5FU administration in an attempt to define the optimal way of utilizing the drug.

Biochemical modulation of 5FU with calcium leukovorin (LV) enhances the intracellular reduced folate pool and prolongs the inhibition of thimidylate synthase by 5FU metabolites LV and 5FU is the most frequently used regimen for metastatic colorectal cancer and has been associated with higher response rates and a trend toward improved survival compared with the single agent bolus 5FU regimen.

A variety of 5FU schedules and LV doses have been used, but two common regimens are recommended

- Bolus 5FU and Leukovorin

Daily for five days: 5FU at 425 mg/m2 preceded by 20 mg/m2 LV daily for 5 days every 4 – 5 weeks.[23]

Weekly: LV 500 mg/m2 infused over 2 hours with 5FU, 600 mg/m2 as an intravenous bolus 1 hour after the start of the LV infusion weekly for 6 weeks, repeated every 8 weeks.[24]

- Continuous infusion of 5-FU

Continuous infusion of 5FU may have efficacy equivalent to that of bolus 5FU and LV[25] and is generally well tolerated, despite the inconvenience of the prolonged intravenous infusion apparatus. 5FU at 300 mg/m2/day is infused continuously by ambulatory infusion pump.

The pattern of 5FU toxicity differs, depending on whether it is administered as a bolus or continuous infusion. Bolus administration has pronounced myelotoxic effects, whereas the dose limiting toxic effects of continuous infusion of 5FU are mucositis and diarrhea. Palmar – plantar erythrodysesthesia (hand – foot syndrome) has been reported with protracted infusions.

Overall the incidence of side effects is significantly lower when 5FU is administered by continuous infusion. A meta-analysis of more than 1200 patients treated with either continuous infusion or bolus regimens of 5FU demonstrated superior response rates and a small survival advantage for the continuous infusions regimens. Continuous infusions of 5FU may have modest activity in patients who have progressed on a bolus 5FU regimen.[26]

b. New agents

Paclitaxel (Taxol), a recently introduced novel microtubule inhibitor, produced minor responses in some patients with advanced colorectal cancer during phase I testing.[27] Phase II studies performed to evaluate paclitaxel efficacy have not demonstrated significant activity in colorectal cancer.[28]

Irinotecan is a topoisomerase I targeting agent with activity in patients with advanced colorectal cancer who have previously been treated with 5FU. Response rates range from 15% to 25%. Irinotecan can be given at 125 mg/m2 infused over 90 minutes weekly for 4 weeks followed by a 2-week rest, or at 350 mg/m2 over 90 min every 3 weeks. Delayed onset diarrhea, nausea, vomiting, and neutropenia are common clinical side effects.

Significant survival advantages have been observed for using irinotecan as second line therapy after 5FU, compared with suggestive care or with continuous–infusion 5FU regimens.

In preliminary studies, the combination of irinotecan and 5FU and LV in untreated patients with colorectal cancer is highly promising. A three-arm randomized phase III study has compared 5FU-LV with irinotecan

alone and with the combination of irinotecan and weekly 5FU and LV.[29] A significantly improved overall response rate was noted for the irinotecan and 5FU combination (33%) compared with 5FU and LV alone (18% $p < 0.001$) or with irinotecan alone (17%). Toxicity was not worse with the combination arm. Another randomized study comparing the same combinations also found a significantly better response rate for the three-drug regimen[30]. The combination of 5FU–LV–irinotecan is likely to be used as the new standard, against which newer agents and regimens will be judged when targeting the treatment of advanced colorectal cancer because of the considerably higher response rates and the longer survival. There results led the FDA to approve this combination as first line treatment for metastatic colorectal cancer in March of 2000.

Other chemotherapeutic agents in development for the treatment of advanced colorectal cancer include TS inhibitors, oral fluorinated pyrimidines, a new platinum analog, and new molecular targeted agents.

Raltitrexed (Tomudex) is a potent, selective inhibitor of TS. It is polyglumated and is retained intracellulary for prolonged periods, allowing for a convenient dosing schedule of a 15-minute infusion repeated every 21 days.

Oral fluorinated pyrimidines: Two oral fluorinated pyrimidines have undergone phase III testing: (1) UFT, a combination of uracil and tegafur, which is administered together with oral leukovorine and (2) capecitabine (Xeloda). Both of these compounds are metabolized to 5FU. The results of phase III studies comparing these two oral fluorinated pyrimidines to IV regimens of 5FU and LV have shown at least comparable efficacy in terms of response rates and survival. The advantages of these oral fluorinated pyrimidines over 5FU include the convenience of oral administration and a favorable toxicity profile. Capecitabine has been found to cause hand-foot syndrome, a toxicity commonly observed with infusional 5FU.[31-33]

Oxaliplatin is a new diaminocyclotrexane platinum compound that is under investigation. Oxaliplatin has demonstrated activity in patients with pretreated, 5FU-resistant colorectal cancer when used alone (10% response rate)[34,35] or in combinations with 5FU (45% response rate).[36,37] In patients with untreated metastatic colon carcinoma, response rates of 18% have been reported with oxaliplatin alone[38,39] and rates as high as 57% when the drug as combined with 5FU. Oxaliplatin's toxicity profile includes nausea, vomiting and cumulative, reversible neuropathy.

Despite the good response rates and favorable time to progression seen in all trials combining oxaliplatin and 5FU, an overall advantage has never been observed. The lack of definitive survival advantage prompted the FDA oncology board to recommend against approval for this agent as first line treatment for colorectal cancer. Clinical trials are still ongoing with this promising new agent, including combination with CPT11.[41,42]

A number of molecular- targeted agents are currently being investigated. The vEGF receptor inhibitor SU5416 and the monoclonal antibodies C225 and rhu MAb-VEGF have reached the later stages of development and been commonly combined with more conventional chemotherapy regimens.

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