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Review

Adjuvant Chemotherapy for Colon Cancer

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Abstract. *Surgery remains the only curative therapy for colon cancer. However, several studies during the last years have proved that systemic chemotherapy in the adjuvant setting definitely improves the curative rate for those patients with localized colon cancer. The combination of 5-fluorouracil (5-FU) and leukovorin (LV) remained the reference treatment for over a decade. However, oxaliplatin-based chemotherapy has emerged as the new standard of care in adjuvant treatment of stage III colon cancer. The role of adjuvant therapy in stage II cancers remains controversial and its routine use is recommended only in high risk patients. This review focuses on the efficacy, safety and toxicity of several drugs used in the adjuvant treatment of colon cancer and on clinical issues, such as the timing for initiation of chemotherapy, its duration and treatment of special patient subgroups, such as stage II or elderly patients.*

Colon cancer is one of the most common malignancies, especially in Western countries, accounting for over a million new cases and about 500,000 deaths per year, worldwide (1).

Surgery is the primary curative modality in patients with localized colorectal adenocarcinoma. However, the risk of recurrence is still high in many patients after potentially curative surgery. Adjuvant chemotherapy for patients with localized colon cancer is used in order to eradicate micrometastases and, therefore, to improve the survival rate after curative surgical resection. Chemotherapy is the principal adjuvant therapy for patients with colon cancer and the addition of radiotherapy has not been shown to improve survival (2). Recent randomized trials, incorporated new drugs, such as capecitabine, irinotecan and oxaliplatin into the adjuvant setting, leading to significant alterations in patient care.

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Fluoropyrimidines

Bolus 5-fluorouracil (5-FU). The issue of adjuvant chemotherapy after surgery in colon cancer remained controversial until the late 1980s. In 1988 a meta-analysis, which included nearly 10,000 patients in 25 randomized trials revealed a small survival benefit in patients receiving adjuvant 5-FU after surgery compared to those who underwent surgery alone (odds ratio, 0.83; 95 % confidence interval [CI], 0.70 to 0.98) (3).

Furthemore, *levamisole (LEV)*, an immunomodulator with mild toxicity, showed a small but statistically significant survival benefit as a single agent in adjuvant therapy. However, these observations were derived from small, poorly controlled trials in the early 1980s (4). The impact of the combination of 5-FU and LEV was tested through a large randomized trial, the Intergroup 0035 (Int 0035) trial, which randomly assigned 1,296 patients with stage B2 or C colon cancer, to observation or to treatment for one year with 5-FU/LEV combination. Patients with stage C disease could also be randomly assigned to treatment with LEV alone. Among patients with stage C disease, the risk of cancer recurrence was reduced by 41% ($p<0.0001$) for the LEV plus 5-FU arm, compared with the observation only arm (5). The overall death rate was reduced by 33% ($p=0.006$). Treatment with LEV alone had no detectable effect. The results in the patients with stage B2 disease were equivocal and allowed no firm conclusions. After a median follow-up of 6.5 years, the data showed no loss of this benefit (6).

Leucovorin (LV) is a reduced folate that increases the antitumor activity of 5-FU through enhancement of the inhibition of thymidylate synthase (7, 8). To evaluate the efficacy of the combination of 5-FU and LV as adjuvant therapy, the National Surgical Adjuvant Breast and Bowel Projects (NSABP) trialists compared a regimen of weekly 5-FU plus high-dose LV (5-FU/LV) to a 5-FU/semustine/vincristine (MOF) combination in 1,081 patients with Dukes' B and C colon cancer (9). Disease-free survival (DFS) and overall survival (OS) were significantly better for patients receiving 5-FU/LV compared with those

receiving MOF (3-year DFS, 73% *vs.* 64%; $p=0.0004$ and 3-year OS, 84%vs 77%; $p=0.003$). The 5-year data showed that the DFS rate in the 5-FU/LV group was 66% *versus* 54% in the MOF group ($p=0.0004$) and the OS rate was 75% in the 5-FU/LV group compared to 66% in the MOF group ($p=0.003$). The International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) pooled data for combined analysis from five separate trials of 5-FU and LV *versus* surgery only in stage II and III colon cancer patients (10). The 5-FU/LV combination significantly reduced mortality by 22% (95% CI 3-38; $p=0.029$) and relapses by 35% (22-46; $p<0.0001$), increasing 3-year relapse-free survival from 62% to 71% and overall survival from 78% to 83%.

The next step was to determine if 5-FU/LV was superior to 5-FU/LEV in the adjuvant setting. In addition, the optimal duration of treatment was in question. An Intergroup study (INT-0089) randomized 3,759 patients with stage III and high-risk stage II colon cancer to 5-FU/LEV for 12 months, weekly 5-FU with high-dose LV (5-FU 500 mg/m^2, LV 500 mg/m^2, Roswell-Park regimen) for 7 to 8 months, 5-FU with low-dose LV (5-FU 425mg/m^2, LV 20 mg/m^2, known as the Mayo Clinic regimen) for 6 months, or 5-FU/LEV for 6 months (11). Results from this trial showed that the: (i) 5-FU/low dose LEV is equivalent to the 5-FU/high dose LV; (ii) 5-FU/LV given for 6 months is as good as given for 12 months; (iii) there is no significant difference between the two most commonly used bolus 5-FU/LV dose schedules: 5-FU 425 mg/m^2 and LV 20 mg/m^2 days 1-5 every 4 weeks for six cycles (Mayo clinic regimen) and 5-FU 500 mg/m^2 and LV 500 mg/m^2 weekly 6 every 8 weeks for three to four cycles (Roswell Park regimen); (iv) 5-FU/LV given for 6 months is inferior to the same treatment given for 12 months. This resulted in the acceptance of 5-FU/LV for 6 to 8 months as the standard treatment for stage III colon cancer since middle of 90's.

Continuous infusion of 5-FU. The next step in the evolution of adjuvant chemotherapy for colon cancer was the evaluation of the 5-FU/LV continuous infusion. Continuous infusion of 5-FU resulted in less hematological toxicities and a small, but statistically significant survival advantage over bolus regimens in advanced CRC, thus, providing the rationale to investigate continuous infusion 5-FU as adjuvant therapy (12).

Continuous infusion of 5-FU has been compared to bolus administration as adjuvant treatment in patients with colon cancer in three randomized phase III trials (13-15). None of these studies yielded a significant difference in terms of DFS and OS in favor of any arm (Table I). However, continuous infusion 5-FU had a more favorable profile concerning toxicity.

Toxicity profile of 5-FU. The toxicity profile of 5-FU is depending on the method of administration. The toxicity of the Mayo Clinic regimen (5-FU 425 mg/m^2 and LV 20 mg/m^2, days 1-5, every 4 weeks) mainly consists of neutropenia and stomatitis. In contrast, with weekly bolus doses, diarrhea is the most common toxic effect. Continuous infusion of 5-FU has a better toxicity profile, with less hematological and gastrointestinal toxicity, but palmar-plantar erythrodysesthesia ("hand-foot syndrome") is more common (16-18). Although regimens involving continuous intravenous infusion were previously perceived as more expensive and less convenient than bolus regimens, recent analyses suggest that differences in cost and quality of life between the bolus and prolonged-infusion schedules are marginal (19, 20).

Oral fluoropyrimidines. Capecitabine (Xeloda) is a prodrug that undergoes a three-step enzymatic conversion to fluorouracil (21). In metastatic colon cancer, capecitabine was proven to offer a small but statistically significant survival benefit, with more favorable toxicity profile (22) and was, therefore, also studied as an adjuvant treatment for patients with resected Dukes' C colon cancer in the X-ACT trial (23). A total of 1,987 patients were randomly assigned to receive the Mayo Clinic regimen or capecitabine 2500 mg/m^2, for two consecutive weeks, followed by one week rest. After a median follow-up period of 3.8 years, capecitabine showed a trend towards superior DFS *versus* 5-FU/LV ($p=0.0528$), and a similar trend to superiority for OS ($p=0.0706$,). Relapse-free survival (RFS) was also superior for capecitabine compared to 5-FU/LV ($p=0.041$). Toxicity profile was in general better for capecitabine, with fewer episodes of grade 3 or 4 neutropenia, febrile neutropenia, or sepsis and stomatitis ($p=0.001$). However, more patients experienced grade 3 hand-foot syndrome than those treated with 5-FU/LV ($p=0.001$). Consequently, capecitabine may be considered as an alternative to 5-FU/LV in the adjuvant therapy of stage III colon cancer patients.

Another orally administered fluorouracil that inhibits dihydropyrimidine dehydrogenase is uracil plus tegafur (UFT). Tegafur, a prodrug of fluorouracil, is combined with uracil, which is a competitive blocker of dihydropyrimidine dehydrogenase, to improve the absorption and bioavailability of tegafur (24). The NSABP C-06 trial compared the administration of UFT in combination with LV, with the bolus 5-FU/LV administration. One thousand, six hundred and eight patients were enrolled and after 5 years of follow-up no difference in terms of efficacy was found (25). A meta-analysis in Japanese population, studied the combination of mitomycin (MMC) and UFT as adjuvant therapy for colorectal carcinoma, compared with surgery alone and indicated that combination treatment with MMC and oral fluoropyrimidines had a survival benefit (26).

Table I. *Randomized studies comparing bolus vs. continuous infusion of 5-fluorouracil (5-FU) as adjuvant treatment for patients with colon cancer.*

Study	Disease stage	No. of pts	Treatment	DFS (%)	*p*-value	OS (%)	*p*-value
GERCOR (13)	II (43%); III (57%)	905	A: Bolus 5-FU (400 mg/m^2)/LV (200 mg/m^2) days 1–5;q4 weeks B: LV5FU Bolus 5-FU (400 mg/m^2) days 1,2 Infused 5-FU (600 mg/m^2) days 1,2 LV (200 mg/m^2) days 1,2;q 2 weeks	67.2 *vs.* 67.7	NS	80 *vs.* 80	NS
SAFFA (14)	II (41%); III (59%)	801	A: Bolus 5-FU (425 mg/m^2)/LV (20 mg/m^2); days 1–5;q 4 weeks B: Infused 5-FU (300 mg/m^2/day) Continuously (3 months)	66.7 *vs.* 73.3	0.10	71.5 *vs.* 75.7	0.08
INTERGROUP 0153 (15)	II (15%); III (85%)	940	A: Bolus 5-FU (425 mg/m^2)/LV (20 mg/m^2) days 1–5;q4 weeks for 3 cycles, then every 5 weeks for 3 cycles/LEV B: Infused 5-FU (250 mg/m^2/day) weeks 1–7 then 1 week's rest/LEV	61 *vs.* 63	0.59	70 *vs.* 69	0.20

DFS: Disease-free survival; OS: overall survival; GERCOR: Groupe coopérateur multidisciplinaire en oncologie; SAFFA: Short Adjuvant Fluorouracil and Folinic Acid Study; LEV: levamisole given 50 mg 8 hourly for 3 days every 2 weeks, LV: leucovorin, NS: non significant.

Combination Chemotherapy in Adjuvant Treatment

Oxaliplatin and irinotecan had made a significant impact in metastatic CRC in recent years. The evaluation of these two agents in the adjuvant setting was therefore a logical step.

Oxaliplatin/5-FU combination. The European Multicenter International study of oxaliplatin/infusional 5-FU/LV [FOLFOX 4] in the adjuvant treatment of Colon Cancer (MOSAIC) study randomized 2,246 stage II and III colon cancer patients to receive 5-FU/LV (LV 200 mg/m^2 followed by 5-FU bolus 400 mg/m^2 and then a 22-hour infusion of 5-FU 600 mg/m^2 given on 2 consecutive days every 14 days, for 12 cycles), or the same 5-FU/LV regimen plus oxaliplatin, (85 mg/m^2). The 3-year DFS was 78.2% in the oxaliplatin/5-FU/LV group and 72.9% in the 5-FU/LV group ($p=0.002$), while the 3-year OS was 87.7% and 86.6%, respectively ($p=$NS) (27). Grade 3 or 4 neutropenia was much commoner in the 5-FU/LV plus oxaliplatin arm than in the 5-FU/LV arm (41.1% *vs.* 4.7%, $p<0.001$), but was complicated by fever or infection in only 1.8% of cases (20 patients) in the 5-FU/LV plus oxaliplatin arm and in 0.2% of cases (2 patients) in the 5-FU/LV group ($p<0.001$). Although 92.1% of patients treated with oxaliplatin/5-FU/LV had peripheral neuropathy during treatment, half of these episodes were considered as grade 1. Grade 2-3 neuropathy was developed in 44%, but 11 patients (1.1%) who were assessed one year after the end of treatment continued to have grade 3 peripheral neurosensory symptoms and this number dropped to five (0.5%) after 18 months.

Furthermore, one recently reported study (NSABP C-07) has also shown that the addition of oxaliplatin to bolus 5-FU/LV significantly improved DFS compared to bolus 5-FU/LV alone. Therefore, oxaliplatin-containing regimen should be considered for all stage III colon cancer patients. However, one should bear in mind that no overall survival advantage has been yet demonstrated in either MOSAIC or NSABP C-07 studies, as data are still maturing.

Irinotecan/5-FU combination. In contrast with the oxaliplatin studies, three randomized trials comparing irinotecan/5-FU combinations with bolus or continuous infusion 5-FU/LV failed to show any benefit in terms of DFS in favor of irinotecan (Table II). This failure could be due to several factors. The definition of DFS could be critical in the failure of the PETACC-3 study (28). This included second non-colorectal cancer as an event in DFS, where this was not included in the MOSAIC study (27). The RFS excluded second non-colorectal cancer and was used as a secondary end-point in the PETACC-3 study. Therefore, RFS in PETACC-3 was identical to DFS in the MOSAIC study. There was indeed a statistically significant improvement in RFS in favor of FOLFIRI (irinotecan/bolus and continuous infusion 5-FU/LV) in the PETACC-3 study. The ACCORD study (29), was powered to show a 15% improvement in 3-year DFS by the use of irinotecan, (from 45% with LV5FU2 to 60% with FOLFIRI) an improvement that was far too optimistic. Thus, the study was underpowered to show any smaller but clinically meaningful differences. Additionally, as with PETACC-3, there was no stratification for T-staging

Table II. *Randomized trials evaluating irinotecan/ 5-fluorouracil (5-FU) combination as adjuvant treatment in colon cancer.*

Study	Disease stage	No. of pts	Treatment	DFS (%)	*p*-value	OS (%)	*p*-value
FNCCLCC ACCORD-2 (29)	High risk stage III	400	A:LV5FU Bolus 5-FU (400 mg/m^2) days 1, 2 Infused 5-FU (600 mg/m^2) days 1, 2 LV (200 mg/m^2) days 1, 2;q 2 weeks	60	0.22	NR	NR
			B: FOLFIRI Irinotecan (180 mg/m^2), day 1 Bolus 5-FU (400 mg/m^2) days 1, 2 Infused 5-FU (600 mg/m^2) days 1, 2 LV (200 mg/m^2) days 1, 2;q 2 weeks	51		NR	
PETACC-3 (28)	III	2111	A: LV5FU Bolus 5-FU (400 mg/m^2) days 1,2 Infused 5-FU (600 mg/m^2) days 1,2 LV (200 mg/m^2) days 1, 2;q 2 weeks	60.3	0.091	NR	NR
			B: FOLFIRI Irinotecan (180 mg/m^2), day 1 Bolus 5-FU (400 mg/m^2) days 1, 2 Infused 5-FU (600 mg/m^2) days 1, 2 LV (200 mg/m^2) days 1, 2;q 2 weeks	63.3		NR	
CALGB 89803 (42)	III	1264	A : 5-FU 5-FU (500 mg/m^2)/LV (500 mg/m^2); weekly x6;q8 weeks	NR	0.80	NR	0.81
			B: Irinotecan (125mg/m^2) 5-FU (500 mg/m^2)/LV (20 mg/m^2); weekly x4;q6 weeks	NR		NR	

DFS: Disease-free survival, OS: overall survival, FNCLCC: Federation Nationale des Centres de Lutte Contre le Cancer, FFCD: Federation Francaise de Cancerologie Digestive, PETACC: Pan-European Trials in Adjuvant Colon Cancer, CALGB: Cancer and Leukaemia Group B, LV: leucovorin, NS: non significant, NR: not reported.

in the randomization process, a parameter that led to a statistically significant imbalance of T4 *versus* T1-3 tumors in both studies. However, T-staging was included as a stratification factor in the MOSAIC study. The CALGB C89803 study used irinotecan/bolus 5-FU/LV (IFL) regimen which had a considerable safety issue (30) and IFL was inferior in efficacy to FOLFOX in advanced CRC (31). Therefore, it can be concluded that irinotecan adjuvant studies performed, thus, far were not adequately designed and the value of irinotecan is still to be proven.

Chemotherapy for Stage II Colon Cancer

The role of adjuvant chemotherapy for stage II colon cancer remains a controversial issue. The relative and absolute benefits of adjuvant chemotherapy in stage II colon cancer have been suggested from a combined analysis from four sequential NSABP trials that compared different adjuvant chemotherapy regimens with each other or with no adjuvant treatment (32). Forty-one percent of the patients included in these four trials had resected Dukes' B tumors. When data from all four trials have been examined in a combined analysis, the mortality reduction was 30% for Dukes' B patients *versus* 18% for Dukes' C patients. The mortality reduction in Dukes' B patients occurred irrespective of the presence or absence of adverse prognostic factors. However, the analysis was criticized for having different treatment and control arms in each study, with none of the studies comparing standard 5-FU/LV chemotherapy to surgery alone.

On the contrary, the IMPACT analysis, which was a pooled analysis of five separate trials that compared 1,016 stage II colon cancer patients randomized to 5-FU/LV (n=507) *versus* observation (n=509) after potentially curative resection, after a median follow-up period of 5.75 years concluded that patients receiving 5-FU/LV did not experience a significant increase in DFS or OS (33). Furthermore, a meta-analysis performed by a Canadian group, based on data from 4,187 patients revealed no significant survival benefit from adjuvant chemotherapy in patients with stage II colon cancer (34). On the other hand, the QUASAR study, a randomized study of 3,238 patients (92% of patients in this study were stage II) showed a significant benefit for stage II patients. With a median follow-up of 4.6 years, adjuvant chemotherapy was

associated with significantly reduced recurrence ($p=0.001$) and improved survival ($p=0.02$). The 5-year recurrence rates were 22.2% for the chemotherapy arm and 26.2% for the observation arm. The 5-year OS rates were 80.3% for the chemotherapy arm and 77.4% for observation arm. Among the patients with stage II colon cancer, the survival benefit for chemotherapy was also significant ($p=0.04$) (35).

The latest guidelines of the American Society of Clinical Oncology (ASCO) do not recommend the routine use of adjuvant chemotherapy in stage II colon cancer, unless there are specific risk factors: poorly-differentiated histology, T4 lesions, bowel perforation and inadequately sampled lymph nodes (n<13) (36). However, with the availability of more effective chemotherapy agents, such as oxaliplatin and irinotecan, more significant benefits (and toxicity) of adjuvant chemotherapy in the treatment of stage II colon patients are possible. In the MOSAIC trial, 40% patients had stage II disease; the 3-year DFS was higher in the patients who received the FOLFOX treatment than those treated with only 5-FU/LV (86.6% *vs.* 83.9%, $p=0.07$) with a relative risk reduction of 18%. The subpopulation analysis suggested an even higher relative risk reduction of 28% in "high-risk" stage II patients who had one or more of the following factors: T4 lesion, obstruction or perforation of the bowel, poor differentiation, or less than 10 lymph nodes examined from surgical specimens (37).

Adjuvant Chemotherapy for Elderly Patients

Clinical trials and patterns of care studies have shown that older patients with localized colon cancer may obtain the same relative benefit as their younger counterparts from adjuvant chemotherapy. In a pooled analysis, based on individual patient data from seven randomized trials (3351 patients), adjuvant treatment had a significant positive effect on both overall survival and time to tumor recurrence ($p<0.001$ for each). No significant interaction was observed between age and efficacy of treatment. The incidence of toxic effects was not increased among the elderly (age >70 years), except for leucopenia in one study. Another large population-based cohort study according to the Surveillance, Epidemiology and End Results (SEER) with 3,357 elderly patients with stage III colon cancer, revealed a 27% reduction of hazard of death for patients receiving 5-FU-based adjuvant chemotherapy. These effects do not diminish with advancing patient age, although competing co-morbidities in the elderly population may reduce absolute survival (38).

When Should Adjuvant Treatment be Started?

The best time to start adjuvant chemotherapy is within 6-8 weeks after surgery. There is evidence that delay in starting chemotherapy beyond this time may have detrimental effect on patient survival. A Swedish study in patients with stage III cancer, reported worse survival for patients who started adjuvant treatment more than eight weeks after surgery, when compared with those who started treatment after less than eight weeks (39). Moreover, the SAFFA trial reported significantly inferior survival for those patients who delayed starting adjuvant chemotherapy more than eight weeks (14).

Conclusion

The percentage of patients with colon cancer receiving adjuvant chemotherapy has increased in more than 60% of patients with stage III colon cancer. Patients receiving adjuvant therapy for stage III colon cancer, especially low-grade cancer, have an increased survival benefit of 16%. Oxaliplatin-based chemotherapy is becoming the standard of care (at least in patients with stage III disease). Irinotecan testing as adjuvant treatment has failed to show any survival benefit and its use should not be routinely recommended. Oral fluoropyrimidines in the adjuvant setting have been proven to be equivalent in terms of efficacy to bolus 5-FU/LV. In terms of safety, a continuous infusion schedule of 5-FU/LV and oral capecitabine has a more favorable safety profile than bolus schedule. For stage II colon cancer, adjuvant therapy remains controversial. High risk patients (intestinal perforation, T4 tumors, poorly-differentiated tumors, inadequately pathologically examined lymph nodes and extramural venous or lymphatic invasion) should be treated with a 5-FU/LV-based chemotherapy. For average risk patients, a discussion of the small benefit of chemotherapy should be made and the patient should be involved in the decision-making process. Oxaliplatin-based combination chemotherapy in stage II colon cancer may consist of an over-treatment, as neurotoxicity can be prolonged and disabling. The standard duration of treatment is six months and treatment should start within 8 weeks after surgery.

Future Perspectives

Several new drugs are now being incorporated into the treatment of colon cancer. Targeted agents, such as cetuximab (40) or bevacizumab (41) have shown significant activity in metastatic disease and the next step in the evolution of adjuvant treatment is to focus on the use of these agents. Additionally, molecular markers, such as microsatellite instability and defects in the DNA mismatch repair system, intratumoral levels of various enzymes involved in fluorouracil activation and metabolism, such as thymidylate synthase, dihydropyrimidine dehydrogenase and thymidine phosphorylase, are used in current clinical trials. The best way to incorporate these potent new therapeutic tools into treatment plans for individual patients remains to be

determined. Furthermore, efforts should be made to develop ways in which therapy can be tailored to individual patients.

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