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Adjuvant Treatment of Colorectal Cancer

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Colorectal cancer (CRC) represents a major public health problem, accounting for more than 1 million new cases diagnosed and about a half million deaths worldwide each year.¹ Despite surgery with curative intent, the risk of recurrence is high. The search for the most effective adjuvant therapy for the eradication of micrometastases is a priority, as is the identification of patients whose tumors are not going to recur after surgery.

Colon Cancer

Postoperative adjuvant chemotherapy with bolus 5-fluorouracil (5-FU) and leucovorin (LV) for patients with high-risk colon cancer was shown to improve patient outcome²⁻⁵ and became the standard of care in the early 1990s. There is no significant difference in efficacy between the two most commonly used bolus 5-FU/LV dose schedules: 5-FU 425 mg/m² and LV 20 mg/m² days 1-5 every 4 weeks for six cycles (Mayo clinic regimen); and 5-FU 500 mg/m² and LV 500 mg/m² weekly × 6 every 8 weeks for three to four cycles (Roswell Park regimen).

Given the better toxicity profile and at least similar efficacy results of continuous infusion 5-FU as compared with bolus 5-FU/LV combinations in metastatic disease, both modalities of treatment were compared in the adjuvant setting. Disease-free survival (DFS) and overall survival (OS) were not statistically different between treatment groups.^{6,7}

Capecitabine, a rationally designed oral fluoropyrimidine that is converted into 5-FU preferentially at the tumor site, could replace infusional 5-FU. Clearly, oral medication obviates the drawbacks of prolonged intravenous (IV) infusion. In 2005, capecitabine was approved in Europe and the United States for the adjuvant treatment of stage III colon cancer after the X-ACT (Xeloda [capecitabine] in Adjuvant Colon Cancer Therapy) trial results became available, showing that capecitabine was at least as effective as intravenous bolus 5-FU/LV (Mayo Clinic regimen) with a better toxicity profile.⁸

Uracil/tegafur (UFT), a 5-FU prodrug, and LV were compared to bolus 5-FU/LV (Roswell Park regimen) in a prospective randomized phase III trial in stage II and III patients. Results showed equivalence in 5-year DFS (68.3% vs. 66.9%) and OS (78.7% vs. 78.7%), with a similar toxicity profile and better quality of life for UFT/LV.⁹

Results clearly demonstrate that capecitabine and UFT/LV can replace bolus 5-FU/LV in the adjuvant treatment of colon cancer.

Irinotecan and oxaliplatin combined with 5-FU have extended survival in patients with metastatic disease. These combinations have also been studied in the adjuvant setting. The two main studies evaluated the safety and efficacy of the combination of 5-FU plus irinotecan as adjuvant therapy for colon cancer. The Cancer and Leukemia Group B (CALGB) study C89803 randomized 1,264 patients with stage III colon cancer to standard treatment with bolus 5-FU/LV (Roswell Park regimen) plus (IFL) or minus irinotecan. The study was prematurely closed due to an excessive number of treatment-related deaths in the IFL arm (2.8%) vs. in the 5-FU/LV arm (0.94%) ($P=.008$). The addition of irinotecan to weekly bolus FU plus LV did not result in improvement in DFS or OS in stage III disease, but did increase both lethal and nonlethal toxicity.¹⁰ The PETACC-3 (Pan-European Trials in Adjuvant Colon Cancer) trial randomized 2,094 stage III colon cancer patients to treatment with two different continuous infusion 5-FU regimens with (FOLFIRI) or without irinotecan. With a median follow-up time of 32 months, the hazard ratio (HR) for DFS was 0.89 (0.77-1.02; $P=.076$; 3-year relapse-free survival, 65.1% vs. 61.8%).¹¹ A French underpowered phase III trial also did not show a

significant benefit for FOLFIRI as compared with LV and bolus plus continuous infusion 5-FU.¹² These results preclude the use of irinotecan in the adjuvant treatment of colorectal cancer.

A regimen of bolus and continuous infusion 5-FU combined with LV was compared with the same regimen plus oxaliplatin (FOLFOX4). A significant improvement in 3-year DFS was observed for the oxaliplatin-containing regimen: 3-year DFS was 72.9% (95% confidence interval [CI], 70.2-75.7) in the 5-FU/LV arm and 78.2% (95% CI, 75.6-80.7) in the FOLFOX4 arm, translating to a 23% reduction in relative risk of recurrence ($P=.002$).¹³ These results prompted the adoption of FOLFOX4 as the new standard treatment for patients with stage III colon cancer. Additional follow-up has demonstrated that the advantage for FOLFOX4 has been maintained.¹⁴ The National Surgical Adjuvant Breast and Bowel Project (NSABP) has reported results from the C-07 trial, which evaluated the addition of oxaliplatin to a weekly Roswell Park regimen of bolus 5-FU and LV (FLOX).¹⁵ The HR (FLOX vs. FULV) was 0.80 (95% CI, 0.69-0.93), a 20% risk reduction with use of FLOX ($P=.004$). Significantly more patients receiving FLOX were hospitalized for diarrhea (5.5% vs. 3%, $P<.01$). Particular care needs to be taken to interrupt and properly adjust treatment for diarrhea. Either the FLOX or the FOLFOX4 regimen can be recommended for use in clinical practice as adjuvant therapy after surgery for stage III and high-risk stage II colon cancer patients defined as medically fit patients with T4 tumors, poorly differentiated histology, bowel perforation presentation, and fewer than 12 lymph nodes sampled.¹⁶

In the adjuvant treatment of stage III colon cancer, a phase III trial comparing capecitabine plus oxaliplatin (XELOX) vs. bolus 5-FU/LV recently completed patient recruitment. So far, only safety findings have been reported.¹⁷

Oxaliplatin-based chemotherapy is now the standard of care in adjuvant treatment of stage III colon cancer. The introduction of monoclonal antibodies targeting epidermal growth factor receptor (EGFR), eg, cetuximab, or vascular endothelial growth factor (VEGF), eg, bevacizumab, has expanded the possibilities for colorectal cancer adjuvant treatment. Anti-VEGF agents have the potential to suppress angiogenesis to prevent

tumor growth and metastasis, while there is improved delivery of anticancer therapy to the tumor to enhance tumor cell killing. Ultimately, anti-VEGF therapy would also disrupt the existing tumor blood supply, further improving the potential to kill tumor cells. Evidence suggests that VEGF and EGFR are potential molecular targets, with separate but overlapping roles in tumor growth and development. In addition to promoting survival and growth of tumor cells, the EGFR appears to affect tumor-associated angiogenesis. Ongoing randomized studies are comparing FOLFOX plus or minus cetuximab and FOLFOX plus or minus bevacizumab. XELOX has also been incorporated, as in the three-arm AVANT trial of adjuvant FOLFOX vs. FOLFOX plus bevacizumab vs. XELOX plus bevacizumab in patients with colon cancer.

Rectal Cancer

Rectal and colon cancer share a common sensitivity to radiation therapy, chemotherapeutic agents, and target-oriented drugs. The anatomic configuration of the pelvis and the close proximity of its organs limit the circumferential margin width when a rectal cancer is surgically excised. To avoid a high local recurrence rate, recommended management includes total mesorectal excision as the optimal surgical approach¹⁸ as well as chemoradiation therapy (CRT) in stages II and III rectal cancer. The possibility of local recurrence is clearly related to the depth of tumor extension through the bowel wall and the presence or absence of nodal involvement. Stage III disease (lymph node involvement) requires adjuvant treatment. In stage II T3N0 rectal cancer, apart from the patient subset with unfavorable factors already described, it would be relevant to identify which patient subgroup will definitely benefit from adjuvant treatment.¹⁹ Stage II T4N0 rectal cancer is primarily not clearly amenable to radical surgery, making such patients suitable candidates for neoadjuvant combined treatment.

The prospective randomized phase III CAO/ARO/AIO 94 (Chirurgische Arbeitsgemeinschaft Onkologie/ Arbeitsgemeinschaft Radioonkologie/ Arbeitsgemeinschaft Interdisziplinäre Onkologie) trial included 823 patients (T3/4 or node-positive). Results confirmed a decrease in toxicity and improved local control with preoperative bolus 5-FU/LV CRT as compared with the postoperative approach.

Sphincter-preserving surgery was performed in 39% and 19% of patients in the preoperative and postoperative settings, respectively ($P=.004$). Overall survival at 5 years was not improved (76% vs. 74%, $P=.8$).²⁰ Similar trials, including the Radiation Therapy Oncology Group (RTOG) 94-01 and NSABP R-03 trials, were prematurely closed due to low recruitment. A preoperative endorectal ultrasound, nuclear magnetic resonance of the pelvis and abdomen, and proper staging procedure must always be performed before administration of neoadjuvant CRT.

In an attempt to improve on the efficacy of 5-FU-based CRT by incorporating more effective drug combinations, a study of XELOX combined with radiotherapy (RT) in T3/4 or node-positive (N+) rectal cancer patients was performed. Preoperative RT (50.4 Gy in 28 fractions) was given concurrently with capecitabine at 1,650 mg/m² on days 1 to 14 and 22-35, and oxaliplatin was administered at 50 mg/m² on days 1, 8, 22, and 29. Surgery was scheduled 4 to 6 weeks after completion of XELOX-RT. Four cycles of adjuvant XELOX (capecitabine 1,000 mg/m² bid on days 1 to 14; oxaliplatin 130 mg/m² on day 1) were administered. Pathologic complete response (pCR), related to DFS, was achieved in 16% of cases, and tumor regression greater than 50% was observed in 50% of them. Grade 3 or 4 diarrhea occurred in 12% of patients.²¹

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