



Davorin RADOSAVLJEVIĆ
Zorica TOMAŠEVIĆ
Ivan POPOV
Svetislav JELIĆ

INSTITUTE FOR ONCOLOGY AND RADIOLOGY OF SERBIA, BELGRADE, SERBIA AND MONTENEGRO

The role of chemotherapy in the management of resectable colorectal cancer

KEYWORDS: Colorectal Neoplasms; Carcinoma; Combined Modality Therapy; Surgery; Chemotherapy, Adjuvant; Antineoplastic Combined Chemotherapy Protocols

ABSTRACT

Adjuvant chemotherapy has been established as the standard of care for patients with node-positive resected colon cancer. 5-fluorouracil modulated with leucovorin given for six months is currently the most widely accepted "standard" regimen. The role of adjuvant chemotherapy in stage II remain investigational and some prognostic indicators that correlate with higher risk for subsequent recurrence may be used for these patients when consider adjuvant chemotherapy. Other investigational approaches include regional, portal vein infusion and intraperitoneal therapy, immunotherapy, and new drugs, with proven activity in metastatic disease. Patients older than 70 years are also candidate for adjuvant therapy of colorectal cancer. Adjuvant chemotherapy of rectal cancer is often associated with radiotherapy and enhances local control seen with radiotherapy and improves survival of these patients.

Address correspondence to:
Davorin Radosavljević, MD, MSc, Institute of Oncology and Radiology of Serbia, Pasterova 14, 11000 Belgrade, Serbia and Montenegro, E-mail: davorr@ncrc.ac.yu

The manuscript was received: 25. 08. 2003.

Accepted for publication: 15.09.2003.

INTRODUCTION

In the management of resectable colon and rectal cancer, surgery is the primary modality, by which the bulk of the disease is removed. The risk of clinical failure following resection of colon cancer is predominantly due to clinical progression of previously undetected distant metastatic disease, and due to residual local disease, in case of rectal cancer. Since we could not identify the patients having residual microscopic disease, prognostic factors that correlate with the probability of micrometastatic disease must be used. The single most important prognostic factor in anticipating the likelihood of residual disease is the stage of the disease: more than 90% patients in stage I will be cured by surgery only, but with stage II and III, the risk of microscopic residual or micrometastatic disease is substantially higher. In those patients adjuvant therapy have to be carefully considered.

ADJUVANT CHEMOTHERAPY OF STAGE III COLON CANCER

Adjuvant chemotherapy for colon cancer was stimulated in the mid of 70's after encouraging results in breast cancer. Once the fluoropyrimidine 5-fluorouracil (5-FU) proved its activity in metastatic disease, clinical studies were begun using this agent in adjuvant setting. Small, underpowered studies from 70's and 80's failed to demonstrate a significant benefit, comparing surgery alone to 5-FU-based chemotherapy following surgery, in stage II and III colon cancer. The first encouraging results were published in 1988 by National Surgical Adjuvant Breast and Bowel Project (NSABP) cooperative group, on 1,166 Dukes' B and C patients randomized to receive MOF chemotherapy after surgery or surgery alone: the patients treated with surgery were in 1.29 times the risk of developing a treatment failure and 1.31 times the risk of dying as were patients receiving chemotherapy (1). Despite some very serious concern, after three patients developed acute leukemia and three myelodysplastic syndromes secondary to semustine, the central role of 5-FU was well recognized, and a search for less toxic regimen was continued.

Levamisol, widely used in veterinary medicine as anthelmintic, had shown *in vitro* immunomodulatory properties, which led to its use in adjuvant regimens for colon cancer, in the mid of the '80s. Levamisole was the subject of almost all big cooperative group trials at the beginning of the 90s: those trials, released from considerable toxicity, finally proved the significance of 5-FU-based adjuvant chemotherapy in high-risk resected colon cancer patients. Levamisol also played a significant role in the large, confirmatory trial conducted through the National Cancer Institute (NCI) Intergroup: 929 eligible patients with stage III and 318 patients with stage II were randomized to receive 5-FU-levamisol vs. levamisol vs. observation. For node-positive (stage III) patients, the 5-year disease-free survival was 44% with surgery alone versus 61% for 5-FU-levamisol arm (2). This highly significant result (39% reduction in mortality with 5-FU-levamisol, $p < 0.0001$, only 6% reduction for levamisol arm) led to the NCI consensus statement in 1990, establishing adjuvant chemotherapy as the standard of care for patients with node-positive resected colon cancer (3). In the above-described study, no benefit was demonstrated in stage B patients. Another agent, leucovorin, given with 5-FU in advanced disease with valuable effects (increased response rate), entered into clinical studies a little bit later. Thus, the last decade was the arena where 5-FU, levamisol and leucovorin were investigated, in the adjuvant setting. What issues were addressed in these studies? First, the priority of 5-FU modulation - levamisol or leucovorin in adjuvant regimens. Second, the duration of chemotherapy - six, eight or twelve months. Third, the dosage of drugs, especially leucovorin. Forth, the schedule of administration - weekly, biweekly or monthly regimens and connected with this the duration of administration - bolus, short infusion or protracted continuous infusion.

NSABP 04 study compared 5-FU-leucovorin vs. 5-FU-levamisol vs. 5-FU-leucovorin + levamisol on 2151 patients, all arms in duration of 12 months: the results of the trial did not show any significant difference in overall and disease-free survival (4). Intergroup trial 0089 included 3759 patients randomized to receive 5-FU-levamisol (12 months) or 5-FU-leucovorin in two differ-



ent schedules (high dose, 8 months and low dose, 6 months) or 5-FU-leucovorin-levamisol (6 months). The results demonstrated that a 6-month treatment with both 5-FU-leucovorin schedules was as effective as the standard 12-month 5-FU-levamisol therapy (Moertel regimen), and showed that the 6-month triple regimen was not superior to 5-FU-leucovorin treatment (5). In QUASAR (Quick and Simple and Reliable) study group from UK, in a 2x2 design, patients received 5-FU plus either high-dose or low-dose of leucovorin in a weekly or monthly schedule, plus levamisol or placebo. The results showed that high-dose leucovorin was not superior to low-dose, and that levamisol had no benefit on survival and recurrence rate (6). In direct comparison of two the most frequently used regimens at the beginning of 90s (5-FU-levamisol "Moertel" vs. 5-FU-leucovorin "Mayo", given for 12 months) in German study, on 702 patients, the authors concluded, after long-term follow-up, that 5-FU-leucovorin is significantly more effective than 5-FU-levamisol (7). From all above-described studies, it could be concluded that 5-FU plus either high-dose (weekly or "Roswell regimen") or low-dose leucovorin (monthly or "Mayo regimen") for six months is currently the most widely accepted "standard" of care for adjuvant treatment of colon cancer. There is no longer a role for the use of levamisol with 5-FU. It is important to mention recently published data using a pooled analysis on 3341 patients who received adjuvant chemotherapy for stage II and III colon cancer. Those patients accrue similar proportional benefits from 5-FU-based adjuvant therapy regardless of age, T and N status, grade, location and gender (8).

ADJUVANT CHEMOTHERAPY OF STAGE II COLON CANCER AND PROGNOSTIC MARKERS

In stage II colon cancer, adjuvant chemotherapy is a matter of debate. American investigators were always much more willing to include these patients in clinical trials, together with node-positive patients. In such trials, the benefit for stage III patients was more obvious than for stage II ones, partly due to insufficient number of patients. Namely, most trials in stage II patients to date have been underpowered to detect the small differences in survival in this group of patients with relatively good prognosis. In IMPACT meta-analysis on 1016 patients (9) in stage II, randomized for 5-FU-leucovorin or surgery alone, the absolute difference in long-time survival was 2% (83% vs. 81%), giving borderline level of significance ($p=0.05$), and in pooled analysis of four NSABP trials (CO 1-4) the relative treatment benefits, in terms of hazard ratios (HRs) were largely the same for stage II and for stage III patients for both overall and disease-free survival (10). NSABP analysis, which was not a true meta-analysis suffered from some methodological inconsistencies: different regimens were used in the chemotherapy arms, and not all the trials used containing surgery-alone control arm. The role of adjuvant chemotherapy in stage II colon cancer remains to be defined by properly powered randomized clinical trials. Patients should be offered chemotherapy only in the context of such studies, or, on occasion, to patients with high risk factors.

Thus, in managing stage II patients, after surgery, some prognostic indicators that correlate with higher risk for subsequent recurrence may be used. These usually include obstruction or perforation of the bowel wall, or invasion of adjacent organs, preoperative elevated carcinoembryonic antigen (CEA) or poorly differentiated tumors, venous or lymphatic invasion or perineural invasion. For all resected colon cancer patients, but particularly for stage II important are the achievements of molecular biology in understanding of the molecular mechanisms of disease: microsatellite instability has been correlated with favorable outcome, loss of heterozygosity at chromosome 18q is a poor prognostic indicator, the thymidilate synthetase expression level inversely correlate with sensitivity and response to 5-FU. Although these molecular analyses may lead to more rational individualization of therapy, we could not at present recommend therapeutic decisions in the routine adjuvant management of colon cancer based on these and other widely investigated markers (ploidy, p53, MIB-1, mismatch repair).

Investigational approaches

Liver is the most common site of colorectal cancer metastases which most likely entering liver via the portal circulation. This is the rationale for regional therapies, including direct portal vein infusion of chemotherapy and intraperitoneal therapy (peritoneal surfaces are also at considerable risk for metastatic disease). This approach counts on high first pass clearance of 5-FU and FUDR, allowing for higher regional doses to be administered than could be tolerated systemically. The largest study, NSABP trial (11), investigating direct portal vein infusion of 5-FU (600 mg/m² daily for 7 days) or surgery alone demonstrated on 1158 patients a modest, but statistically significant improvement in disease-free survival (74 vs. 64% at 4 years), but the development of liver metastases was similar between the two groups. With single course of intraportal chemotherapy, the Swiss Group for Clinical Research (SAKK), showed improved overall survival, but without reduction in hepatic metastases (12). A meta-analysis from 1997, involving more than 4000 patients in randomized trials demonstrated a minimal improvement (4%) in 5-year overall survival (13). At the same time, two large randomized studies, from EORTC (14) and UK (15) failed to show a benefit from intraportal chemotherapy. The conclusion, after more than 10 years of the concept of short-term intraportal adjuvant chemotherapy is that this approach remains investigational and should not be incorporated into standard care.

An investigational approach in adjuvant treatment of colon cancer is also immunotherapy. Using active specific immunotherapy (ASI), combination of BCG and preparation of their own irradiated tumor cells, Vermorken et al. reported superior free-free survival on 170 patients in stage II randomized to surgery alone or with ASI, but with no benefit regarding overall survival (16). Another strategy under investigation is a "prime and boost" vaccination strategy using recombinant vaccinia virus-CEA followed sequentially by a recombinant avipox virus-CEA vaccine, and also a strategy of developing an idiotypic monoclonal antibody vaccine that mimics CEA. All these strategies remain investigational, and large-scale phase III are planned. Edrecolomab, a murine monoclonal immunoglobulin IgG2a directed against the 17-1A epitope, after demonstrated *in vitro* activity against human colon cancer xerografts in nude mice showed, in randomized study, compared with surgery alone, on 166 patients significant difference in long-term survival (57 vs. 37% after 7 years follow-up). The results of confirmatory, phase III trial of 2761 patients with stage C colon cancer, randomized to receive 5-FU-leucovorin plus edrecolomab vs. edrecolomab alone vs. 5-FU-leucovorin were far less encouraging: 3-year survival rates of both 5-FU-containing arms were superior to that of the edrecolomab alone (17).

Irinotecan, oxaliplatin and oral fluoropyrimidines, agents widely used in the management of metastatic colorectal cancer, have now entered randomized clinical trials in the adjuvant setting against 5-FU-leucovorin. It remains unclear should the improved efficacy seen with irinotecan or oxaliplatin in the metastatic setting translate into improved survival in adjuvant setting. Preliminary results of MOSAIC, one of the large, randomized trials (oxaliplatin plus 5-FU-leucovorin vs. 5-FU-leucovorin) on 2246 patients, reported on ASCO this year showed superiority of combination over 5-FU-leucovorin in disease-free survival rate ($p<0.01$) and a 23% decrease in the risk for recurrence (18). With a median follow-up of 37 months, the overall survival rate has not yet been determined. Definitive conclusion could be drawn after reporting definitive results of the trial, including toxicity, acute and long-term ones. The results of other adjuvant trials investigating new drugs are awaiting with hope that new drugs could represent an advance in the adjuvant treatment of colon cancer.

COLORECTAL CANCER IN ELDERLY

Median age of newly diagnosed colorectal cancer patient is nowadays 70 years, and those patients are also candidates for adjuvant chemotherapy. In one survey, conducted in Germany, on 407 patients in Dukes' C, only 47% of

patients over 70 years received adjuvant chemotherapy (19). A meta-analysis on 3351 patients was performed to examine the value of adjuvant chemotherapy in elderly patients (over 70 years). The results demonstrated the benefit of adjuvant therapy consistent across all age groups, and no significant age-treatment interaction was observed. The authors concluded that the benefit of treatment was not age-dependent (20). Thus, elderly patients that are otherwise fit for chemotherapy should receive this treatment after resection of a high-risk colon or rectal cancer.

ADJUVANT CHEMOTHERAPY OF RECTAL CANCER

The rate of local recurrences for rectal cancer is higher than for colon cancer and that is why the role of chemotherapy in adjuvant treatment of resectable rectal cancer is very often considering together with radiotherapy. The candidates for radio/chemotherapy are patients with T3 and T4 tumors (Dukes' B2 and B3) and patients with nodal involvement (N1 and N2 i.e. Dukes' C1-3). Radiotherapy, as recommended by ESMO Minimum Clinical Recommendations (21), is postoperative 50 Gy, and chemotherapy is 5-FU-based, concomitant with radiotherapy, if preoperative radiotherapy has not been given. 5-FU-based chemotherapy may be continued for 2-4 months following radiotherapy. In these radio/chemotherapy-combined modalities, radiotherapy decreases local recurrence and chemotherapy further enhances local control seen with radiotherapy and improves survival. Radiotherapy issues (long-lasting US-Scandinavian dilemma: postoperative or preoperative radiotherapy) are closely associated with the type of surgery required and the possibilities of sphincter-preserving operations.

Chemotherapy schedules, investigated in the last decade, included bolus 5-FU regimens and on the other hand protracted infusion of 5-FU, given concurrently with radiotherapy and before and after radiotherapy. NCCTG/Intergroup study (NCCTG 864751) revealed, on 660 patients a survival advantage for infusional 5-FU over bolus injection ($p=0.005$) when 5-FU was delivered by prolonged venous infusion (PVI) during radiotherapy (22). Addressing important issues of biochemical modulation of 5-FU, and the duration of chemotherapy administration, Intergroup 0114 conducted phase III trial of 5-FU-based chemotherapy regimens plus radiotherapy, comparing PVI during radiotherapy vs. PVI before and after radiotherapy vs. biochemically modulated 5-FU which avoided central lines. On 1917 patients, and after median follow-up of 4.6 years, relapse-free and overall survival was similar in all three arms (RFS 68%-69%, OS 81%-83% at 3 years). The authors concluded that any of these 3 arms are acceptable for clinical practice. Toxicity profiles were slightly different (23).

Do we really need tri-modality treatment for all patients with resectable rectal cancer, or it may be excessive treatment for some of them, tried to answer authors from NSABP, pooling five phase III trials, on 3745 evaluable patients. They divided patients into intermediate risk (T1-2 N1 and T3N0), moderately high (T1-2 N2 and T4N0 and T3N1) and high risk (T3 N2 and T4 N1-2) and concluded that tri-modality treatment may be excessive for all patients with intermediate risk. They also recommend future trials designed to evaluate separate regimens for intermediate vs. moderately high or high-risk patients (24).

REFERENCES

1. Wolmark N, Fisher B, Rockette H, Redmond C, Wickerham DL, Fisher ER et al. Postoperative adjuvant chemotherapy or BCG for colon cancer: Results from NSABP Protocol C-01. *J Natl Cancer Inst* 1988;80:30-6.
2. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Goodman PJ et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990;322:352-8.
3. NIH Consensus Conference: Adjuvant therapy for patients with colon and rectal cancer. *JAMA* 1990;264:1444-50.
4. Wolmark N, Rockette H, Mamounas E, Jones J, Wieand S, Wickerham DL et al. Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin and levamisole in patients with Dukes' B and C carcinoma of the colon: Results from national surgical adjuvant breast and bowel project C-04. *J Clin Oncol* 1999;17:3553-9.
5. Haller DG, Catalano PJ, MacDonald JS, Mayer RJ. Fluorouracil (FU), leucovorin (LV) and levamisole (LEV) adjuvant therapy for colon cancer: Five-year final report of INT-0089. *Proc Am Soc Clin Oncol* 1998;17:256a (abstr).
6. Kerr DJA. United Kingdom coordinating committee on cancer research study of adjuvant chemotherapy for colorectal cancer: Preliminary results. *Semin Oncol* 2001;28 Suppl 1:31-4.
7. Arkenau HT, Bermann A, Rettig K, Strohmeyer G, Porschen R. 5-fluorouracil plus leucovorin is an effective adjuvant chemotherapy in curatively resected stage III colon cancer: long-term follow-up results of the adjCCA-01 trial. *Ann Oncol* 2003;14:395-9.
8. Gill S, Loprinzi L, Sargent DJ, Haller DG, Benedetti J, Francini G et al. Using a pooled analysis to improve the understanding of adjuvant therapy (AT) benefit for colon cancer (CC). *Proc Am Soc Clin Oncol* 2003;22:253a (abstr.)
9. International Multicenter Pooled Analysis of B2 Colon Cancer Trial (IMPACT B2) Investigators: Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer. *J Clin Oncol* 1999;17:1356-63.
10. Mamounas E, Wieand S, Wolmark N, Bear HD, Atkins JN, Song K et al. Comparative efficacy of adjuvant chemotherapy in patients with Dukes B versus Dukes C colon cancer: Results from four national surgical adjuvant breast and bowel project adjuvant studies. (C-01, C-02, C-03, C-04) *J Clin Oncol* 1999;17:1349-55.
11. Wolmark N, Rockette H, Wickerham DL, Fisher B, Redmond C, Fisher ER et al. Adjuvant therapy of Dukes' A, B and C adenocarcinoma of the colon with portal vein fluorouracil hepatic infusion: Preliminary results of National Surgical Adjuvant Breast and Bowel Project Protocol C-02. *J Clin Oncol* 1990;8:1466-75.
12. Swiss Group for Clinical Cancer Research: Long term results of single course of adjuvant intraportal chemotherapy for colorectal cancer. *Lancet* 1995;345:349-52.
13. Liver Infusion Meta-analysis Group: Portal vein chemotherapy for colorectal cancer: A meta-analysis of 4000 patients in 10 studies. *J Natl Cancer Inst* 1997;98:497-505.
14. Rougier P, Sahnoud T, Nitti D, Curran D, Doci R, De Waele B et al. Adjuvant portal-vein infusion of fluorouracil and heparin in colorectal cancer: A randomized trial. *Lancet* 1998;351:1677-81.
15. James RD. Intraportal 5-FU (PVI) and peri-operative radiotherapy in the adjuvant treatment of colorectal cancer (CRCa) - 3681 patients randomized in the UK Coordinating Committee on Cancer Research (UKCC-CR) AXIS trial. *Proc Am Soc Clin Oncol* 1999;18: 264a (abstr.)
16. Vermorken JB, Claessen AM, van Tinteren H, Gall HE, Ezinga R, Meijer S et al. Active specific immunotherapy for stage II and III colon cancer: A randomized trial. *Lancet* 1999;353:345-50.
17. Punt CJ, Nagy A, Douillard JY, Figer A, Skovsgaard T, Monson J et al. Eprexolomab alone or in combination with fluorouracil and folinic acid in the adjuvant treatment of stage III colon cancer: A randomized study. *Lancet* 2002;360:671-7.
18. De Gramont A, Banzi M, Navarro M, Tabernero J, Hickish T, Bridgewater J et al. Oxaliplatin - 5-FU - LV in adjuvant colon cancer: Results of the international randomized mosaic trial. *Proc Am Soc Clin Oncol* 2003;22:253a (abstr.)
19. Grothey A, Buchele T, Feigl-Lurz L et al. Survey-based analysis of treatment algorithms in colorectal cancer (CRC) in Germany discloses deficits in patients care. *Proc Am Soc Clin Oncol* 2000:17.
20. Sargent D, Goldberg R, Macdonald J et al. Adjuvant chemotherapy for colon cancer (CC) is beneficial without significantly increased toxicity in elderly patients (Pts): Results from a 3351 Pts meta-analysis. *Proc Am Soc Clin Oncol* 2000:18.
21. ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of rectal cancer. *Ann Oncol* 2003;14:1006-7.
22. O'Connell MJ, Martenson JA, Wieand HS, Krook JE, Macdonald JS, Haller DG et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med* 1994;331:502-7.
23. Smalley SR, Benedetti J, Williamson S, Robertson J, Fisher B, Martenson J et al. Intergroup 0144 - phase III trial of 5-FU based chemotherapy regimens plus radiotherapy (XRT) in postoperative adjuvant rectal cancer. Bolus 5-FU vs prolonged venous infusion (PVI) before and after XRT + PVI vs bolus 5-FU + leucovorin (LV) + levamisole (LEV) before and after XRT + bolus 5-FU + LV. *Proc Am Soc Clin Oncol* 2003;22:251a (abstr 1006).
24. Gunderson LL, Sargent D, Tepper J, Wolmark N, O'Connell M, Begovic M et al. Impact of TN stage and treatment on survival and relapse in adjuvant rectal cancer pooled analysis. *Proc Am Soc Clin Oncol* 2003;22:251a (abstr 1008).