Pergamon

*European Journal of Cancer*, Vol. 34, No. 11, pp. 1652–1663, 1998

Printed in Great Britain
0959-8049/98/$—see front matter

PII: S0959-8049(98)00251-2

# Current Controversies in Cancer

# Is There a Standard Adjuvant Treatment for Colon Cancer?

M.L. Slevin and D. Papamichael | P. Rougier | H.J. Schmoll

## *Pro:*

M.L. Slevin and D. Papamichael

Department of Medical Oncology, St Bartholomew's Hospital, London EC1A 7BE, U.K.

### BACKGROUND

Adenocarcinoma of the colon and rectum is the second most common cause of cancer death in Western societies. Although many patients present with what are considered to be resectable tumours, a large number will go on to die from recurrent/metastatic disease. Approximately 60 000 people die from colorectal adenocarcinomas among the 150 000 new cases which are diagnosed in Europe each year.

Adjuvant chemotherapy and, in cases of rectal cancer, the addition of radiotherapy are aimed at increasing the overall survival of patients at high risk of recurrence after resection of the primary tumour. Radiotherapy and combined modality treatments (chemoradiotherapy) usually reserved for the management of rectal cancer will not be considered further in this article. For more than three decades there has been controversy about the use of adjuvant treatment programmes in colon cancer. Early adjuvant studies testing single agent systemic chemotherapy failed to show a significant increase in survival [1–5]. Four adjuvant studies in the late 1970s and early 1980s tested systemic chemotherapy with 5-fluorouracil (5-FU) and lomustine with (MOF) or without oncovin [6–9], only one of them demonstrating a significant benefit in terms of survival [9]. In 1988, the first meta-analysis reporting on adjuvant chemotherapy in colorectal cancer was published. It concluded that, overall, regimens that contained 5-FU added a small benefit in terms of overall survival, with an odds ratio of 0.83 (95% confidence interval, CI 0.70–0.98).

### 5-FU AND MODULATING AGENTS

With the uncertainty surrounding the effectiveness of bolus 5-FU therapy, a number of investigators started looking at the use of modulating agents. Levamisole (LEV), a phenylimidothiazole compound, is an antihelminthic agent with immunomodulatory activity (T-cell stimulation) [10], that has no effect on survival when used alone adjuvantly [11]. The concurrent administration of 5-FU and LEV was first tested in the advanced disease setting with one trial showing an improvement in median survival as compared with the 5-FU alone arm [12], although two subsequent trials failed to confirm this [13, 14]. Despite these reports, interest in LEV continued. The first Intergroup study of adjuvant 5-FU and LEV was initiated in 1984, and by 1989 the 3-year survival data were reported [15]. On the basis of a reduction in the relapse rate by 40% and mortality by one third for the 5-FU/LEV arm, the National Cancer Institute (NCI) concluded that "the therapeutic option of post-surgical observation ('no treatment' control groups) is no longer justifiable for NCI-sponsored adjuvant studies for Dukes' C patients" [16]. The final report of the Intergroup trial confirmed the early observations [17]. For the last 6–7 years, this treatment has been considered as standard for patients with Dukes' C disease in North America. Despite these results, there has been considerable debate about the efficacy of treatment, especially in Europe, where studies with a no treatment control arm have continued. However, recent preliminary data from the Dutch adjuvant chemotherapy trial using the same chemotherapy regimen, show a significant survival advantage at 26 months' follow-up, for both Dukes' B and C patients, although not for rectal cancer patients (F.A. Zoetmulder). Three-year data from this study will be available shortly.

The combination of 5-FU and leucovorin (LV) has proved superior to 5-FU alone in patients with advanced colorectal cancer [18]. A number of studies have since confirmed the efficacy of 5-FU modulated by LV as adjuvant treatment, when compared with a no treatment control arm [19–22]. The NSABP (National Surgical Adjuvant Breast and Bowel project) protocol C0-3 indicated a disease free (73% versus 64%) and overall (84% versus 77%) survival advantage for the 5-FU/LV combination when compared with MOF (lomustine, oncovin, 5-FU) at 3 years for patients with Dukes' stage B and C colon cancer [19]. The control arm in

Correspondence to M.L. Slevin.

this study (MOF) had previously shown a survival advantage in the adjuvant setting [9]. The Canadian and European consortium trial (IMPACT) compared adjuvant treatment with high-dose 5-FU and LV with no treatment in nearly 1500 patients: they demonstrated a 22% reduction in mortality at 3 years, both in Dukes' B and C patients [20]. A similar in design but smaller Italian study showed a 39% reduction in mortality for the same group of patients [21]. With a median follow-up duration of 72 months, an Intergroup study indicated that patients who received a combination of 5-FU and low dose LV over 6 months experienced significant improvement in time to relapse ($P < 0.01$) and survival ($P = 0.02$) compared with control patients treated with surgery alone [22].

More recent reports from the NSABP protocol C0-4 [23], and a collaborative trial of the NCCTG (North Central Cancer Treatment Group) and the National Cancer Institute of Canada (NCIC) [24] suggest that 5-FU/LV is probably superior to 5-FU/LEV. The NSABP C0-4 indicated that the 5-FU/LV combination was at least as effective and possibly had a disease free and overall survival advantage in patients with Dukes' B and C colon cancer, when compared with 5-FU/LEV. The NCCTG/NCIC study showed that survival for 6 months of the 5-FU/LEV group was significantly inferior to the group that received 5-FU/LV/LEV for the same duration. Preliminary results of trial INT-0089 showed that no additional benefit appears to be gained from the addition of LEV when 5-FU/LV is given [25].

As yet there are no studies indicating a role for the modulation of 5-FU by interferon in the adjuvant setting, although a number of randomised studies in patients with advanced disease show no benefit either in terms of response rates or survival [26–28].

## INFUSIONAL VERSUS BOLUS 5-FU

In addition to modulating the activity of 5-FU by agents such as LV and alpha-interferon, the pharmacology of 5-FU may be altered by prolonged infusional therapy. Two main features distinguish all the bolus schedules from the infusional ones: different toxicities occur and much higher-dose intensities are possible when 5-FU is given as a continuous infusion. Bolus schedules produce leucopenia, mucositis and diarrhoea, whereas infusional schedules are usually complicated by mucositis and dermatitis (plantar/palmar erythema). A phase III trial by Anderson and Lokich demonstrated improved response rates for the infusional schedule compared with standard bolus therapy in advanced colorectal cancer [29]. The 'De Gramont regimen' [30] which is popular in northern Europe as well as the U.K. was randomised against the 'Mayo regimen' in patients with advanced colorectal cancer [31]. The De Gramont regimen combines bolus with infusional 5-FU and was found to be more effective, with an increased progression free survival and significantly less toxicity. There was no difference in terms of survival between the two regimens. This regimen has not yet been tested in the adjuvant setting.

## PORTAL VEIN AND INTRAPERITONEAL CHEMOTHERAPY

The use of a continuous infusion of fluoropyrimidines into the liver via the portal vein, for 1 week during the immediate postoperative period, has been supported by the theoretical advantage that with this approach, for the many patients who will develop hepatic micrometastases, infusional 5-FU may provide a higher-dose intensity within the liver. A recently published meta-analysis of 4,000 patients in 10 studies showed encouraging results for this approach, indicating an improvement in 5-year survival for patients treated with portal vein infusion [32]. This confirms the results of an earlier meta-analysis which showed a significantly lower mortality for patients treated with portal vein infusion (13% risk reduction; $P = 0.02$) [33].

Another interesting technique currently under investigation in the adjuvant treatment of colorectal cancer is intraperitoneal chemotherapy, in combination with systemic treatment. Such an approach would have the potential advantage of acting on both microscopic peritoneal tumour spread as well as on liver micrometastases, since intraparitoneal 5-FU is absorbed through the portal vein and results in a high 5-FU concentration in the portal blood. Although the benefit of such an approach is not proven, a small randomised study from investigators in Austria indicates a possible advantage over conventional adjuvant therapy. Patients with resected Dukes' B or C colon cancer were assigned to either intravenous and intraperitoneal 5-FU/LV or intravenous 5-FU/LEV as the 'standard therapy' arm. A preliminary analysis after a median follow-up time of 27 months showed a significant disease free survival advantage in favour of the experimental arm (17/94 versus 35/96 recurrences, $P = 0.0015$) [34].

## DUKES' B COLON CANCER

It is more difficult to detect a survival advantage in Dukes' B patients, as the number of events is smaller and large numbers of patients are required. The Intergroup study of 5-FU/LEV for Dukes' B2 patients suggested a decreased relapse rate for the treatment group, but without a significant improvement in survival [35]. However, a review of the comparative efficacy of adjuvant chemotherapy for patients with stage II disease from four NSABP studies, concluded that ''Dukes' B colon cancer patients receive at least as much relative benefit from adjuvant chemotherapy as Dukes' C, and should be offered that treatment'' [36]. An event free but not overall survival benefit for Dukes' B patients was shown in the IMPACT trial [20].

## TREATMENT DURATION

The study describing the combination of 5-FU and LEV by Moertel and colleagues [17], as most other studies including LEV adjuvantly, have had a treatment duration of 1 year. In studies in which a combination of 5-FU and LV was used, the drugs were mostly given for 6 months [19–22]. This treatment duration would appear to be at least as effective [23].

## IMMUNOTHERAPY

A growing interest in the immunological treatments of malignancy has led to the development of both specific and non-specific immunotherapy adjuvant trials in colorectal cancer. One of the first studies (NSABP C-01) had a three arm randomisation to either no postoperative therapy, MOF chemotherapy, or intradermal BCG. At 5 years' follow-up, the BCG treatment group demonstrated a slight survival advantage compared with surgery alone, although there was no difference in terms of disease free survival in the two groups [37]. A study by the ECOG (Eastern Cooperative

Oncology Group) revised in 1990 after the 5-FU and LEV data in 1989, randomly assigned Dukes' C patients to either receive 'standard' 5-FU/LEV chemotherapy, or chemotherapy and active specific immunotherapy. The results of this study are awaited.

The adjuvant use of monoclonal antibodies (MAb) has recently attracted much interest after the publication of the 7-year follow-up data for treatment with the murine MAb 17-1A [38]. This demonstrated a reduction in mortality rate for the antibody arm of 32% and in recurrence rate of 23%. There was a significant overall survival advantage for the antibody arm ($P < 0.01$).

## CONCLUSIONS

Significant progress has been made in recent years in the adjuvant treatment of colorectal cancer. There is now overwhelming evidence to support the use of adjuvant chemotherapy in patients with Dukes' C colon cancer. Patients with Dukes' B tumours also appear to derive a definite but smaller absolute benefit. Adjuvant treatment programmes are now firmly established as part of the standard management of patients in this setting. New chemotherapeutic agents with interesting activity in colorectal cancer, as well as the increasing use of immunotherapy in addition to conventional treatments, offer further opportunities to improve results. The prediction of chemosensitivity for individuals by assessing the expression of proteins such as p53, thymidylate synthase (TS) and bcl-2 may also enhance our ability to optimise treatment [39–41].

The body of evidence presented here suggests that adjuvant chemotherapy for Dukes' C and high risk Dukes' B patients is standard treatment. The optimal regimen should probably be a combination of 5-FU and LV for a duration of 6 months. The combination of 5-FU/LEV for 1 year is a reasonable alternative.


1. Rousselot LM, Cole DR, Grossi CE, *et al.* Intraluminal chemotherapy (HN2 of 5-FU). Adjuvant to operation for cancer of the colon and rectum. *Cancer* 1967, **20**, 829–833.
2. Grossi CE, Wolf WI, Nealon TF, *et al.* Intraluminal fluorouracil chemotherapy adjuvant to surgical procedure of resectable carcinoma of the colon and rectum. *Sur Gyn Obst* 1977, **145**, 549.
3. Lawrence W, Terz JJ, Horsley S, *et al.* Chemotherapy as an adjuvant to surgery for colorectal cancer. *Ann Surg* 1975, **181**, 616–623.
4. Dixon WJ, Longmire WP, Holden WD. Use of triethylenethiophosphoramide as an adjuvant to the surgical treatment of gastric and colorectal carcinoma: ten year follow-up. *Ann Surg* 1971, **173**, 26–39.
5. The Veterans Administration Surgical Adjuvant Cancer Chemotherapy Group. Adjuvant use of HN2 (NSC-762). Progress report. *Cancer Chemother Rep* 1965, **44**, 27–30.
6. Higgins GA, Amadeo JH, McElhinney J, *et al.* Efficacy of prolonged intermittent therapy with combined 5-fluorouracil and methyl-CCNU following resection for carcinoma of the large bowel. *Cancer* 1984, **53**, 1–8.
7. Panettiere FJ, Goodman PJ, Costanzi JJ, *et al.* Adjuvant therapy in large bowel adenocarcinoma: long-term results of a Southwest Oncology Group Study. *J Clin Oncol* 1988, **6**, 948–954.
8. Mansour EG, McIntyre JW, Johnson R, *et al.* Adjuvant studies in colorectal carcinoma: experience of the Eastern Cooperative Oncology Group (ECOG). Preliminary report. In Gerard A, ed. *Progress and Perspectives in the Treatments of Gastrointestinal Tumours.* New York, Pergamon Press, 1981, 68–75.
9. Wolmark N, Fisher B, Rockette H, *et al.* Post-operative adjuvant chemotherapy or BCG for colon cancer: results from NSABP protocol C-01. *J Natl Cancer Inst* 1988, **80**, 30–36.
10. Tripodi D, Parks LC, Brugmans J. Drug-induced restoration of cutaneous delayed hypersensitivity in anergic patients with cancer. *N Engl J Med* 1978, **289**, 354–357.
11. Arnaud JP, Buyse M, Nordlinger B, *et al.* Adjuvant therapy of poor prognostic colon cancer with levamisole: result of an EORTC double-blind randomized clinical trial. *Br J Surg* 1989, **76**, 284–289.
12. Davis T, Borden E, Wolbert W, *et al.* Levamisole and 5-fluorouracil in metastatic colorectal carcinoma (Abstract). *Proc ASCO* 1982, **1**, Abstract 396.
13. Buroker T, Moertel C, Fleming T, *et al.* A controlled evaluation of recent approaches to biochemical modulation or enhancement of 5-fluorouracil therapy in colorectal carcinoma. *J Clin Oncol* 1985, **3**, 1624.
14. Mansour EG, Cnaan A, Davis T, *et al.* Combined modality therapy following resection of colorectal carcinoma in patients with non-measurable intra-abdominal metastases. An ECOG study 3282 (Abstract). *Proc ASCO* 1990, **9**, Abstract 412.
15. Moertel CG, Fleming TR, Macdonald JS, *et al.* Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990, **332:**, 352–358.
16. Anonymous. The efficacy and the group C status of levamisole and 5-fluorouracil for patients with Dukes' C colon cancer. National Cancer Institute Update, October 1989.
17. Moertel CG, Fleming TR, Macdonald JS, *et al.* Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. *Ann Intern Med* 1995, **122**, 321–326.
18. Advanced Colorectal Cancer Meta-analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol* 1992, **10**, 896–903.
19. Wolmark N, Rockette H, Fisher B, *et al.* The benefit of leucovorin modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from NSABP C-03. *J Clin Oncol* 1993, **11**, 1879–1887.
20. Anonymous. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT). *Lancet* 1995, **345**(8955), 939–944.
21. Francini G, Petrioli R, Marsili S, *et al.* Folinic acid plus 5-fluorouracil as adjuvant chemotherapy in colon cancer. *Proc ASCO* 1994, **13**, Abstract 571.
22. O'Connell MJ, Mailliard JA, Kahn MJ, *et al.* Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. *J Clin Oncol* 1997, **15**, 246–250.
23. Wolmark N, Rockette H, Mamounas EP, *et al.* The relative efficacy of 5-FU + leucovorin (5-FU-LV), 5-FU + levamisole (LEV), and 5-FU + LV + LEV (5-FU-LV-LEV) in patients with Dukes' B and C carcinoma of the colon: first report of NSABP C-04. *Proc ASCO* 1996, **14**, Abstract 460.
24. O'Connell MJ, Laurie JA, Shepherd L, *et al.* A prospective evaluation of chemotherapy duration and regimen as surgical adjuvant treatment for high risk colon cancer: a collaborative trial of the North Central Cancer Treatment Group and the National Cancer Institute of Canada Clinical Trials Group. *Proc ASCO* 1996, **14**, Abstract 478.
25. Haller DG, Catalano PJ, *et al.* Eastern Cooperative Oncology Group (ECOG), Southwest Oncology Group (SWOG), Cancer and Acute Leukaemia Group B (CALGB fluorouracil, leucovorin and levamisole adjuvant therapy for colon cancer: preliminary results of INT-0089. *Proc ASCO* 1996, **14**, Abstract 486.
26. Seymour MT, Slevin ML, Kerr DJ, *et al.* Randomized trial assessing the addition of interferon alpha-2a to fluorouracil and leucovorin in advanced colorectal cancer. Colorectal Cancer Working Party of the United Kingdom Medical Research Council. *J Clin Oncol* 1996, **14**(8), 2280–2288.
27. Hill M, Norman A, Cunningham D, *et al.* Royal Marsden Phase III trial of fluorouracil with or without interferon alfa-2b in advanced colorectal cancer. *J Clin Oncol* 1995, **13**, 1297–1302.
28. Greco FA, Figlin R, York M, *et al.* Phase III study to compare interferon alfa-2a in combination with fluorouracil versus fluorouracil alone in patients with advanced colorectal cancer. *J Clin Oncol* 1996, **14**, 2674–2681.

29. Anderson N, Lokich JJ. Cancer chemotherapy and infusional scheduling. *Oncology* 1994, **8**, 99–116.
30. De Gramont A, Krulik M, Cady J, *et al.* High dose folinic acid and 5-fluorouracil bolus and continuous infusion in advanced colorectal cancer. *Eur J Cancer Clin Oncol* 1988, **24**, 1499–1503.
31. de Gramont A, Bosset J-F, Milan C, *et al.* Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. *J Clin Oncol* 1997, **15**, 808–815.
32. Anonymous. Portal vein chemotherapy for colorectal cancer: a meta-analysis of 4000 patients in 10 studies. *J Natl Cancer Inst* 1997, **89**, 497–505.
33. Piedbois P, Buyse M, Gray R, *et al.* Portal vein infusion is an effective adjuvant treatment for patients with colorectal cancer. *Proc ASCO* 1995; **14**, Abstract 444.
34. Scheithauer W, Marczell A, Depisch D, *et al.* Combined intravenous and intraperitoneal chemotherapy with 5-fluorouracil (5FU) and leucovorin versus 5-FU and levamisole for adjuvant therapy of resected colon carcinoma. *Proc ASCO* 1996, **14**, Abstract 507.
35. Moertel CG, Fleming TR, Macdonald JS, *et al.* Intergroup study of fluorouracil plus levamisole as adjuvant therapy for stage II/ Dukes' B2 colon cancer. *J Clin Oncol* 1995, **13**(12), 2936–2943.
36. Mamounas EP, Rockette H, Jones J, *et al.* Comparative efficacy of adjuvant chemotherapy in patients with Dukes'B vs Dukes' C colon cancer: results from four NSABP adjuvant studies (C-01, C-02, C-03, C-04). *Proc ASCO* 1996, **14**, Abstract 461.
37. Wolmark N, Fisher B, Rockette H, *et al.* Postoperative adjuvant chemotherapy for BCG for colon cancer: results from NSABP protocol C-01. *J Natl Cancer Inst* 1988, **80**, 30–36.
38. Riethmuller G, Holz E, Schlimok G, *et al.* Monoclonal antibody (Mab) adjuvant therapy of Dukes C colorectal carcinoma: 7-year update of a prospective randomized trial. *Proc ASCO* 1996, **14**, Abstract 1385.
39. Peters GJ, van der Wilt CL, van Groeningen CJ, *et al.* Thymidylate synthase inhibition after administration of fluorouracil with or without leucovorin in colon cancer patients: implications for treatment with fluorouracil. *J Clin Oncol* 1994, **12**(10), 2035–2042.
40. Johnston PG, Fisher ER, Rockette HE, *et al.* The role of thymidylate synthase expression in prognosis and outcome of adjuvant chemotherapy in patients with rectal cancer. *J Clin Oncol* 1994, **12**(12), 2640–2647.
41. Zhao-Shi Zeng, Sarkis AS, Zuo-Feng Zhang, *et al.* p53 nuclear overexpression: an independent predictor of survival in lymph node-positive colorectal cancer patients. *J Clin Oncol* 1994, **12**(10), 2043–2050.

**PII: S0959-8049(98)00252-4**

# *Contra:*

P. Rougier

Hôpital Ambriose Paré, Department of Gastro-entérology, 9, ave Charles de Gaulle, 92100 Boulogne cedex, France

COLORECTAL CANCER is estimated to rank third in incidence in men in Europe, it is the second most frequent cancer in women and approximately 60 000 people will die from colorectal adenocarcinomas among the 150 000 new cases which will be diagnosed this year. Adjuvant treatment aims at increasing life expectancy, especially of people at high risk of recurrence after resection of colon carcinoma Astler-Coller stage B2 and C [1], or UICC stage II and III [2]. After more than 30 years of efforts, the results of recently published large randomised trials have given important indications on what adjuvant treatment to administer and whom it will benefit. However, there is no single standard treatment, but many efficient protocols, and clinicians and patients have to choose which will be the more appropriate in each case.

The combination of 5-fluorouracil (5-FU) and levamisole was the first efficient adjuvant chemotherapy for colon cancer Dukes' stage C curatively resected (Table 1). In 1990, Moertel and colleagues reported a very significant benefit for Dukes' C patients receiving a 1 year combination of weekly 5-FU and biweekly oral levamisole [5]. After that publication, this combination was considered as the standard adjuvant treatment for colon cancer [7], but many physicians, especially in Europe, were not convinced for many reasons:

- The combination of 5-FU and oral levamisole is no more active than 5-FU alone in metastatic patients, but is more toxic;
- There is no clear explanation for the mechanism of action of 5-FU and oral levamisole;
- Oral levamisole has no antitumour activity in randomised trials [6, 8];
- There was no 5-FU alone arm in the INT 0035 trial and it is possible that the positive results reported by Moertel and colleagues were to the 5-FU efficacy alone and, if the previous adjuvant trials using 5-FU alone were individually not effective, this was in part related to the small number of patients included. A meta-analysis has demonstrated that there was a significant benefit when all these trials using 5-FU were analysed together [9].
- More active combinations of 5-FU were known at this time, especially with leucovorin or methotrexate in metastatic patients [10, 11];
- The survival rate of the control group was abnormally low (around 40% at 5 years) and the quality of the 'radical' surgery has been questioned by many surgeons thinking that a better quality of surgical excision very significantly increase the control group survival rate and decrease the need for adjuvant chemotherapy; presently there is an ongoing trial in The Netherlands which aims to reproduce the INT 0035 trial results.

Because, since 1984 the combination of 5-FU and leucovorin has been known to be effective in metastatic colorectal