Pergamon

European Journal of Cancer Vol. 30A, No. 5, pp. 578–579, 1994

0959-8049/94 $7.00+0.00

0959-8049(93)E0051-5

Adjuvant Treatment of Colon Cancer. A Plea for a Large-scale European Trial

J. Wils, H. Bleiberg and Ph. Rougier

UNTIL 1988 adjuvant chemotherapy for colorectal cancer was felt by the vast majority of oncologists to be of no advantage. Results of different randomised studies failed to demonstrate any therapeutic benefit [1–5]. However, in 1988 and 1989 two large Cooperative Group trials showed a significant benefit for adjuvant chemotherapy in colon cancer [6, 7].

The tide changed definitively when the results of the Intergroup study became available [8, 9], although different views were taken by European oncologists [10] and the response initially was more conservative.

The evidence that adjuvant therapy is effective in colon cancer is now confirmed by the results of recently completed trials, presented at the American Society of Clinical Oncology (ASCO) meeting in 1993, that compared 5-fluorouracil (5-FU)/leucovorin for 6 months with control [11, 12].

Furthermore, the National Surgical Adjuvant Breast and Bowel Project (NSABP) compared in its successor study, C-03, 5-FU/leucovorin with MOF (methyl-CCNU, vincristine, 5-FU) in Dukes' B/C colon cancer, and reported a significant survival benefit for 5-FU/leucovorin at 3 years, with an equal benefit in stages B and C [13].

The prolonged disease-free survival obtained with 5-FU/leucovorin in these trials appeared to be in the same magnitude as that obtained with 5-FU/levamisole in the Intergroup study. These results also suggest that 6 months of adjuvant treatment is probably sufficient and that 5-FU plus leucovorin might be at least equivalent to 5-FU plus levamisole.

As a consequence of these studies, the evidence that systemic adjuvant 5-FU-based treatment can delay or reduce recurrence after resection of high-risk (Dukes' C or TNM stage III) colon cancer is now compelling [14].

Results from ongoing or closed US studies (Intergroup 0089 and NSABP C-04), that accrued over 5000 patients and compared 5-FU/leucovorin with 5-FU/levamisole and with the combination of the three drugs, will address the question of the more optimal chemotherapy, and are awaited with interest.

Portal vein infusion of cytotoxic drugs is another method of adjuvant treatment that was popularised by Taylor and colleagues at the University of Liverpool, U.K. [15]. Results of different randomised studies that attempted to confirm the positive initial data were inconsistent and the value of this treatment modality so far remains controversial [16]. A meta-analysis has been performed on updated results of completed trials with adjuvant intraportal chemotherapy, but not including the closed study of the European Organization for Research and Treatment of Cancer (EORTC). Data show a significant survival benefit of therapy (survival odds ratio = 0.77) but, somewhat surprisingly, no effect on the incidence of liver metastases [17]. Another review of intraportal studies yielded essentially the same results with a reduction in overall mortality of 31% [18]. This suggests a systemic effect of intraportal infusion which might be due merely to the timing of chemotherapy. Alternatively, one might argue that it is difficult to see how a lower systemic level of 5-FU would be more effective in suppressing distant metastases. It can be hypothesised that intraportal chemotherapy would be more effective for cells "in transit" but not for micrometastases already present in the liver at the time of operation and vascularised by the hepatic artery. Results of randomised studies, conducted in Australia-New Zealand and in Switzerland by the SAKK (Swiss Group for Clinical Cancer Research), that compared perioperative systemic chemotherapy with chemotherapy via the intraportal route, should provide an answer to this question.

Because of the benefit obtained with one cycle of "early" perioperative chemotherapy, this treatment modality, either locally directed by the intraportal or intraperitoneal route, or by the intravenous route, appears to be of high interest in colon as well as in rectal cancer. The question is whether this benefit reduces the benefit obtained with systemic chemotherapy, or whether there is an additional or even synergistic effect.

In March 1993, the EORTC Gastrointestinal (GI) Tract Cooperative Group in cooperation with the Foundation Française de Cancérologie Digestive (FFCD) launched a study (GI 40911) in which the main question is whether "early" locally directed postoperative treatment has an additional benefit when combined with "late" systemic chemotherapy. Early postoperative treatment will be administered either via the intraportal or via the intraperitoneal route, depending on the instutition's experience. Systemic chemotherapy is either "standard" 5-FU/levamisole or 5-FU plus L-leucovorin, both to be administered for 6 months (Figure 1). Patients with rectal cancer are also eligible for this study, whether or not they receive additional radiotherapy. This trial is open to individual investigators or to national groups.

To detect an increase in the median duration of survival of

Correspondence to J. Wils at the Laurentius Hospital, Roermond, The Netherlands. H. Bleiberg is at the Insitut Jules Bordet, Brussels, Belgium; and Ph. Rougier is at the Institut Gustave Roussy, Villejuif, France. Further information concerning participation in this trial can be obtained at the EORTC Data Center, 83 Av E. Mounier, 1200 Brussels, Belgium. Data Manager: Ann Marinus R.N.
Revised and accepted 27 Jan. 1994.

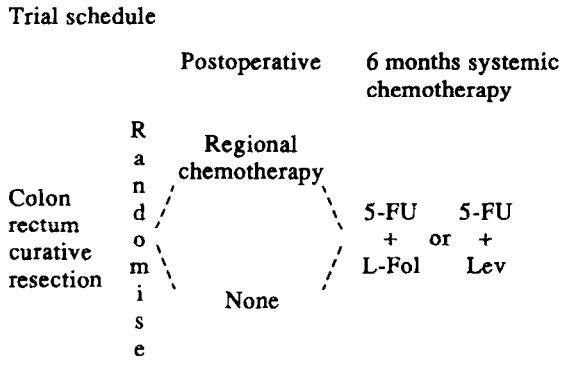

Figure 1. Schedule of EORTC trial Gl 40911. Rectum: radiation should be administered either before surgery, or, if not, decision for postoperative radiotherapy should be made prior to randomisation. 5-FU, 5-fluorouracil. L-Fol, levo-folinic acid; Lev, levamisole (see protocol for exact drug dosages).

30%, 2000 patients need to be randomised. The hope is that this will become the largest trial ever conducted in Europe on this subject. Oncologists in Europe can only compete with US investigators by conducting large-scale international studies with original rationale, and not with small regional or even national studies that merely try to reproduce American data.

Therefore, the EORTC trial with its original design should be strongly supported, and European investigators can more effectively contribute to progress in the adjuvant treatment of colorectal cancer by entering their patients in this study.

1. Gastrointestinal Tumor Study Group. Adjuvant therapy of colon cancer—results of a prospectively randomized trial. *N Engl J Med* 1985, **312**, 1465–1472.
2. Panettierre FJ, Goodman PJ, Constanzi JJ, *et al.* Adjuvant therapy in large bowel adenocarcinoma: long-term results of a Southwest Oncology Group study. *J Clin Oncol* 1988, **6**, 947–954.
3. Higgins GA Jr, 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.
4. Abdi EA, Harbora D, Hanson J, *et al.* Adjuvant chemoimmuno and immunotherapy in stage B_2 and C colorectal cancer. *Proc Am Soc Clin Oncol* 1987, **6**, 93.
5. Mansour E, Ryan L, Lerner H, *et al.* Lack of effectiveness of 5-FU + methyl CCNU as compared to 5-FU for adjuvant therapy in colon cancer. *Proc Am Soc Clin Oncol* 1989, **8**, 115.
6. Wolmark N, Fisher B, Rockette H, *et al.* Postoperative adjuvant chemotherapy or BCG for colon cancer: results from NSABP protocol C-01. *J Natl Cancer Inst* 1988, **80**, 30–36.
7. Laurie JA, Moertel CG, Fleming TR, *et al.* Surgical adjuvant therapy of large bowel carcinoma: an evaluation of levamisole and the combination of levamisole and 5-fluorouracil. A study of the North Central Cancer Treatment Group (NCCTG) and the Mayo Clinic. *J Clin Oncol* 1989, **7**, 1447–1456.
8. Moertel CG, Fleming TH, Macdonald JS, *et al.* Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990, **322**, 352–358.
9. Moertel C. Fleming T, Macdonald J, *et al.* The Intergroup study of fluorouracil (5-FU) plus levamisole (LEV) and levamisole alone as adjuvant therapy for stage C colon cancer. A final report. *Proc Am Soc Clin Oncol* 1992, **11**, 161.
10. Wils JA, Wagener DJTh. Adjuvant treatment of colon cancer. Where to go from here? *Ann Oncol* 1990, **1**, 329–331.
11. O'Connell M, Maillard J, MacDonald J, *et al.* An Intergroup trial of intensive course 5FU and low dose leucovorin as surgical adjuvant therapy for high risk colon cancer. *Proc Am Soc Clin Oncol* 1993, **12**, 190.
12. Zaniboni A, Erlichman C, Seitz JF, *et al.* FUFA increases disease-free survival (DFS) in resected B2C colon cancer (CC): results of a prospective pooled analysis of 3 randomized trials (RCTs). *Proc Am Soc Clin Oncol* 1993, **12**, 191.
13. Wolmark N, Rockette H, Fisher B, *et al.* The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. *J Clin Oncol* 1993, **11**, 1879–1887.
14. Cunningham D, Findlay M. The chemotherapy of colon cancer can no longer be ignored. *Eur J Cancer* 1993, **29A**, 2077–2079.
15. Taylor I, Machin D, Mullee M, *et al.* A randomized controlled trial of adjuvant portal vein cytotoxic perfusion in colorectal cancer. *Br J Surg* 1985, **72**, 359–363.
16. O'Connell MJ. Is portal-vein fluorouracil hepatic infusion effective colon surgical adjuvant therapy? *J Clin Oncol* 1990, **8**, 1454–1456 (editorial).
17. Buyse M. Current status of adjuvant therapy of colon carcinoma. *Abstr Int Conf on Biol and Treatm of Gastrointest Malign.* Frankfurt/Main, 1992, February 4–7, 55.
18. Gray R, James R, Mossman J, *et al.* AXIS. A suitable case for treatment. *Br J Cancer* 1991, **63**, 841–845.

European Journal of Cancer Vol. 30A, No. 5, pp. 579–580, 1994
Elsevier Science Ltd
Printed in Great Britain

Pergamon

0959-8049(94)E0119-O

Adjuvant Treatment of Colon Cancer

I. Taylor

WILS AND COLLEAGUES (pp. 578–579) make a plea for large trials to determine the efficacy of adjuvant treatment in colon cancer—and who could possibly disagree. There is no shortage of small or moderate sized trials and these have appeared at regular intervals since the early 1960s. However, controversy still exists. Even though meta-analyses and overviews demonstrate a probable benefit for certain regimes, the degree of magnitude is likely to be modest at best. Single large trials are still required and the results of on-going ones awaited with great interest. To demonstrate a moderate (10%) improvement in survival will require randomisation of several thousand patients whereas most available studies have included only a few hundred patients, and

Correspondence to I. Taylor at the Department of Surgery, University College London Medical School, 67–73 Riding House Street, London WIP 7LD, U.K.
Received 28 Jan. 1994; accepted 18 Feb. 1994.