Eur J Cancer, Vol. 29A, No. 15, pp. 2077–2079, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00

The Chemotherapy of Colon Cancer can no Longer be Ignored

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COLORECTAL CANCER is a leading cause of death in Europe and the U.S.A., where over 300 000 new cases are diagnosed each year. The primary treatment is surgical resection, but over half the patients will eventually die of metastatic disease, which includes approximately 25% of patients who have evidence of metastases at the time of diagnosis. For patients with resected disease, the risk of relapse depends on the site of the tumour, its size and differentiation, the presence of vascular or neural invasion in the primary tumour, and spread to the lymphatic system. Approximately 50% of patients with regional lymph node involvement (Dukes stage C) will relapse, and the risk is proportional to the number of lymph nodes containing cancer. Where the primary tumour has penetrated the serosa but not spread to the nodes (Dukes stage B), the risk of relapse is less, but up to 25% of patients will die of systemic disease. Both of these groups of patients are candidates for adjuvant chemotherapy, but the results of randomised trials reported in the 1970s and 1980s showed no advantage. However, in 1990, the Intergroup published their results, showing significant improvements in survival by treating patients with Dukes stage C carcinoma of the colon with 12 months of 5-fluorouracil (5FU) and levamisole [1]. On the basis of these results, the National Cancer Institute issued a statement that this treatment should now be standard practice following surgery in Dukes stage C carcinoma. The response in Europe was more conservative, although gradually this approach has gained acceptance, particularly following the presentation of the updated results of the trial at the American Society of Clinical Oncology (ASCO) in 1992. By that time, with a median follow-up of 5 years and an estimated 99.1% of recurrences, and 85% of cancer deaths recorded, there had been 141 (45%) cancer deaths in the surgery alone group of 315 patients compared to 100 (33%) cancer deaths in the 304 patients randomised to 5FU and levamisole. This represents a 32% reduction in the cancer death rate ($P < 0.004$) [2].

At the 1993 ASCO meeting, three additional randomised trials of adjuvant chemotherapy in colon cancer were presented, showing an improvement in relapse-free survival and/or survival with adjuvant 5FU and folinic acid in Dukes stage B and C colon cancer [3–5] (Table 1). The National Surgical Adjuvant Breast and Bowel Project (NSABP) study (C-01) showed a significant survival benefit for 5FU and folinic acid given for 48 weeks when compared to MOF (5FU, semustine and vincristine), and there was no interaction between Dukes stage and benefit [3]. A further Intergroup trial, with a no treatment control arm, which was prematurely closed in 1989 because of the results of the 5FU and levamisole trial, showed a 13% reduction in the relapse rate following 6 months of 5FU and folinic acid [4]. Similar results were compared from an overview of three trials, two from Italy and one from Canada [5].

So where are we now? For patients with Dukes stage B or C colon cancer, the benefits of adjuvant systemic chemotherapy are compelling; on current data it is likely to produce an overall improvement in survival of about 10–15%, which is equivalent to adjuvant endocrine and chemotherapy in premenopausal women [6] except, in colorectal cancer, there is a plateau on the survival curve. Twelve months of 5FU and levamisole has the best track record, but many patients find the duration of treatment onerous. The North Central Cancer Treatment Group (NCCTG) (894651) have randomised 800 patients to 6 or 12 months of chemotherapy, and the results are awaited. Meanwhile, the precise role of levamisole (in the U.S.A. 12 months treatment costs approximately 1000 US dollars), when given in combination with 5FU and folinic acid, needs to be addressed, and the optimal schedule of 5FU and folinic acid requires further elucidation. The Intergroup (INT009) and the NSABP (C-04) have accrued over 4000 patients into trials which will hopefully answer these questions. At the moment, the most cost-effective option is 6 months of 5FU and folinic acid using the 5-day schedule of 5FU 425 mg/m^2 and folinic acid 20 mg/m^2 every 4 weeks, as outlined in the Intergroup protocol [4]. The dose limiting toxicity of this schedule is stomatitis, the incidence of which can be significantly reduced by oral cryotherapy—sucking ice cubes begining 5 min before 5FU and continuing for 30 min [7]. Selecting patients most likely to benefit from adjuvant chemotherapy has always been a problem. However, predicting relapse based on the molecular profile of the primary tumour may be possible in the future [8, 9]. Using age as a criterion for giving adjuvant chemotherapy has always been fraught with difficulty—for example, the average life expectancy of a healthy 75-year-old North American is 10 years [10].

Are there options to systemic chemotherapy? Perioperative chemotherapy given through the portal vein was first reported to improve survival in colorectal cancer by Taylor [11]. He gave a 7-day continuous infusion of 5FU 1 g/day through the portal vein, using a cannula inserted at the time of surgery. In the treatment group of 117 patients, there were 26 deaths compared to 54 deaths in the 127 patients in the control group. This approach has the advantage of being of short duration, cheap and relatively non-toxic. However, subsequent trials have not confirmed such a large impact on survival [12–14]. Moreover, caution must be taken when interpreting the results of the portal vein infusion trials. Data must be analysed on an intention to treat basis. In particular, patients with liver metastases detected at laparotomy should not be excluded from analysis because this may bias the treatment group; insertion of the cannula in the portal vein is likely to be associated with a more careful inspection of the liver and, therefore, the detection of otherwise occult liver metastases. This stage-migration effect could account for the apparently improved survival of Dukes stage B and C tumours. An overview of these data is under way, and the results of two large trials from the U.K. Co-ordinating Committee on Cancer

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Received 12 Aug. 1993; accepted 1 Sep. 1993.

Table 1. Adjuvant chemotherapy in colon cancer

Study group	Dukes stage	Median follow-up (months)	Chemotherapy	Number of patients	Percentage recurrence-free (%)	Number of deaths	Survival (%)
Intergroup	Colon C	60	Control	315	53	153	51
ASCO 1992 [2]			5FU and levamisole 12	304	37	108	64
			months		$P < 0.0001$		$P < 0.005$
NSABP*	Colon B and C	47	MOF	522	64	145	77
ASCO 1993 [3]			5FU/FA weekly × 6	579	73	101	84
			every 8 weeks		$P < 0.0004$		$P = 0.003$
Intergroup	Colon B and C	42	Control	158	64	44	71
ASCO 1993 [4]			5FU 425 mg/m^2	151	77	40	75
			FA 20 mg/m^2 for six cycles		$P = 0.004$		$P = 0.13$
Meta-analysis	Colon B and C	22	Control	758	65		
ASCO 1993 [5]			370–400 mg/m^2 folinic acid	739	74	Follow-up too short	
			200 mg/m^2 for five cycles		$P = 0.001$		

*No interaction between Dukes stage and benefit. MOF, semustine, vincristine, 5FU; FA, folinic acid.

Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC) are awaited. However, on the basis of published information, portal vein infusion is unlikely to produce an equivalent survival benefit to adjuvant systemic chemotherapy, but it may have an additive effect to systemic chemotherapy. Giving 5FU via the portal vein during the perioperative period does not appear to reduce the evidence of liver metastases but could be important, for example, in the eradication of cells shed into the blood stream during surgery—one recent study reported 32% of patients with colorectal cancer have cells of epithelial origin in the bone marrow just prior to surgery [15].

As with adjuvant chemotherapy, the use of chemotherapy in advanced disease differs between North America and Europe. In the U.S.A., most patients with advanced disease will be offered palliative chemotherapy whereas in Europe symptomatic care without cytotoxic drugs is often adopted, and therapeutic nihilism is not uncommon. Are the sceptics views justified? It has always been relatively difficult to objectively assess the benefits of palliative chemotherapy because tumour regression is relatively unusual (no better than 20–30%), and randomised studies of chemotherapy compared to best supportive care were notable by their absence. But recently two randomised trials, one from Scandinavia [16] and one from Austria [17], have shown that systemic chemotherapy approximately doubles the median survival (5 vs. 11 months) of patients with metastatic colorectal cancer. The Vienna study also addressed quality of life, and demonstrated that chemotherapy plus best supportive care resulted in a better quality of life than best supportive care alone, for those patients with abnormal quality of life measurements before starting treatment. Moreover, the Nordic randomised trial demonstrated that pre-emptive chemotherapy resulted in better survival and prolongation of the asymptomatic period, when compared to delaying chemotherapy until symptoms develop.

On the basis of these data, there does at least appear to be a place for discussing the option of chemotherapy with patients who have metastatic colorectal cancer. If, after discussion, a decision to give chemotherapy is taken, what is the best chemotherapy? Firstly, there is no advantage in using combination chemotherapy. Single-agent 5FU remains the mainstay of treatment. Adding other drugs merely increases toxicity, and may lead to a reduction in the amount of 5FU that can be administered. Biochemical modulation of 5FU by folinic acid produces improved response rates (20–30% versus 10–15%) over 5FU alone, but is not associated with an overall improvement in survival [18], except possibly in patients with "unmeasurable disease"—a surrogate for the low tumour burden [19]. In clinical practice, 5FU and folinic acid, given according to the 5-day schedule outlined in the adjuvant treatment section, is the most cost-effective option. The weekly schedule of 5FU and folinic acid may be more convenient in some situations, but is is considerably more expensive and, in one randomised trial, was associated with more frequent in-patient admissions due to toxicity than the 5-day low-dose folinic acid schedule [20]. Continuous low-dose 5FU 300 mg/m^2 is another effective way of giving 5FU. It is relatively non-toxic, and neutropenia and diarrhoea are unusual. Curiously, about 25–30% of patients develop plantar palmar erythema which often responds to pyridoxine. Treatment normally continues for 22 weeks with a 2-week gap on week 10. Symptomatic responses occur in over 80% of patients with this approach, and very little time is spent in hospital or visiting clinics [21]. Objective responses to this regimen are of the same order as 5FU and folinic acid.

Other modulations of 5FU have been investigated. After the initial promise from a phase II trial [22] of bolus 5FU modulation by interferon α, our own unpublished phase III study has failed to confirm a benefit. However, a possible role for interferon α in the reversal of resistance to low-dose infusional 5FU has been identified using magnetic resonance spectroscopy [23], but this needs to be confirmed in randomised trials. Other 5FU modulators, such as *N*-phosphon-acetyl-L-aspartate (PALA), are of biochemical interest but their clinical application is so far limited. On failure of 5FU, second-line therapy is often inappropriate and unlikely to be successful. In one small study, dipyridamole has been used to modulate 5FU resistance as front-line therapy in pancreatic cancer, where it produced a 31% complete response rate [24] and this may be worth studying in patients with resistant colorectal cancer. Other cytotoxic drugs, such as mitomycin-C, can be tested in this setting but objective

responses are in the 5–15% range. The camptothecin analogue, CPT-11, the topoisomerase I inhibitor, is the best new drug on the horizon [25]. It is effective in relapsed patients, and once its optimal schedule is established, it should be investigated in the adjuvant setting.

Advances in the adjuvant treatment of colorectal cancer should result in improved cure rates. Recognition of the role of cytotoxic drugs in the palliation of symptoms and prolongation of survival is long overdue, and will result in improved quality of life for many patients with advanced disease.

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