Efficacy of adjuvant fluorouracil and folinic acid in colon cancer

International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators

Summary

The role of fluorouracil and folinic acid and adjuvant therapy for colon cancer is not clear. We undertook independently three randomised trials to find out the efficacy of fluorouracil and high-dose folinic acid after surgery for Dukes' B and C stage colon cancer. The three studies by the Gruppo Interdisciplinare Valutazione Interventi Oncologia (GIVIO), the National Cancer Institute Canada Clinical Trials Group (NCIC-CTG), and the Fondation Française de Cancerologie Digestive (FFCD) were pooled for combined analysis.

Each trial was multicentre and used the same treatment regimen (fluorouracil 370–400 mg/m^2 plus folinic acid 200 mg/m^2 daily for 5 days, every 28 days for 6 cycles). A pooled analysis of the results was done on the basis of a previously agreed protocol when there were sufficient events to detect at least a 10% reduction in mortality with 80% power. 1526 patients with resected B (56%) and C (44%) carcinoma of the colon were enrolled and 1493 were confirmed as eligible. 736 were assigned to the treatment group and 757 to the control group. Fluorouracil/folinic acid significantly reduced mortality by 22% (95% CI 3–38; p=0·029) and events by 35% (22–46; p<0·0001), increasing 3-year event-free survival from 62% to 71% and overall survival from 78% to 83%. Compliance with treatment was good; more than 80% of patients completed the planned treatment. Side-effects were clinically acceptable with only 1 treatment-related death. The commonest side-effects were gastrointestinal, but severe toxic effects (WHO grade 4) occurred in fewer than 3% of cases.

We conclude that fluorouracil plus high-dose folinic acid is a well-tolerated and effective 6-month adjuvant regimen for colon cancer.

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Introduction

Adenocarcinoma of the colon affects about 1 in 20 people in developed countries and represents one-sixth of all cancers.[1] Fluorouracil is the most active single agent in the treatment of advanced colon cancer. However, investigations of fluorouracil-based adjuvant therapy did not show significant benefits in survival[2] until a trial of MOF (fluorouracil, vincristine, methyl-chloroethyl-cyclohexyl-nitrosourea [methyl-CCNU]) in patients with Dukes' B and C colon cancer showed a reduction in mortality of 24% compared with surgery; however, this regimen was very toxic and had long-term leukaemogenic effects.[3] The combination of fluorouracil with levamisole reduced mortality by 33% in Dukes' C colon cancer compared with surgery alone.[4,5] Results for Dukes' B cancer are not yet available. This combination is much less toxic than MOF and has no leukaemogenic effects. These findings led the US National Cancer Institute to convene a consensus conference, which recommended fluorouracil plus levamisole as standard treatment for Dukes' C colon cancer.[6] As a consequence, most trials of adjuvant systemic treatment in Dukes' C patients that did not offer this combination as standard treatment were prematurely closed.

The cytotoxic activity of fluorouracil is potentiated by folinic acid.[7] An individual data meta-analysis of ten randomised clinical trials comparing folinic-acid-modulated fluorouracil with fluorouracil alone in patients with metastatic colorectal cancer,[8] showed superiority of the combination in terms of response. On the basis of such results several combinations of folinic acid and fluorouracil were chosen as the experimental treatment in many adjuvant trials.

We became aware of three cooperative group trials on the efficacy of a specific high-dose folinic acid and fluorouracil regimen in Dukes' B and C colon cancer patients—Gruppo Interdisciplinare Valutazione Interventi Oncologia (GIVIO; protocol SITAC-01), National Cancer Institute Canada Clinical Trials Group (NCIC-CTG; protocol C-03), and Fondation Française de Cancerologie Digestive (FFCD; protocol 8802). The principal investigators of the three trials decided to conduct a pooled analysis of their data. This approach has been used in studies of neurological disorders.[9]

Patients and methods

Collaborative analysis protocol

In October, 1991, representatives of the three groups wrote the protocol for the pooled collaborative analysis.[10,11] The protocol established criteria for pooling study patients in one common dataset; standard definitions and codings for events and patients' characteristics; the minimum clinical difference to be tested in the main hypothesis and the required statistical power, duration of follow-up, and appropriate timing for the main comparisons; and the analytical approach. During 1992, a common database

*IMPACT investigators listed at end of paper

Correspondence to: Dr S Marsoni, Istituto Mario Negri, Laboratory of Cancer Clinical Epidemiology, Via Eritrea 62, 20157 Milan, Italy

	GIVIO	NCIC-CGT	FFCD
Recruitment			
Date of first randomisation	January, 1989	May, 1987	October, 1982
Total randomised	888	370	268
Eligibility criteria			
Tumour site*	Colon	Colon	Colorectal†
Dukes' stage	B and C	B and C	B and C
Age limit	None	None	75 years
Performance status ECOG	≤2	≤2	≤2
Chemotherapy to start by day	35	56	35
Treatment			
Fluorouracil	370 mg/m² in 50 mL normal saline	370 mg/m² in 50 mL normal saline	400 mg/m² in 100 mL 5% glucosate
Folinic acid	200 mg/m², 10 min before fluorouracil	200 mg/m², 10 min before fluorouracil	200 mg/m², before fluorouracil
Dose adjustments			
Escalations	No	Yes	No
Suspensions	Any grade 4 side effects; grade 3 repeated	Grade ≥3 gastrointestinal side effects	Any grade ≥3 side effects
Reductions			
For bone-marrow side effects	Day 28	Lowest and day 28	Day 28
For gastrointestinal side effects	Grade 3	Grade 3 after day 5	Grade ≥2
Quality assurance			
Eligibility check at randomisation	Yes	Yes	Yes
Visiting programme	No	Yes	No
Central review of surgery and pathology			
Forms	No	Yes	No
Operative samples sides	No	Local reference pathologist	No

*Definition of colon limits FFCD. >12 cm from anal margin; GIVIO, NCIC-CTG colon and proximal rectum covered by peritoneum. †Randomisation stratified by site; for this analysis only colon patients included. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Trial outlines**

was set up and verified when investigators from the three data centres visited each other. In November, 1992, the principal investigators and statisticians of each trial finalised the conduct of the pooled collaborative analysis. A first analysis limited to event-free survival was done in March, 1993.[12] The first analysis on survival is presented here.

Trial designs

Each trial randomised patients by telephone through its own head office. In all three trials randomisation was done after surgery and was stratified by centre and stage of disease. Baseline information and follow-up were the same in the three trials. Eligibility criteria are reported in table 1. All the trials allowed entry of patients with intestinal obstruction for which radical surgery would be needed.

All three trials used a regimen of fluorouracil 370–400 mg/m² plus folinic acid 200 mg/m² daily for 5 days, every 28 days for 6 cycles. The racemic form of folinic acid (leucovorin) was initially used, but the racemic mixture was not available in Italy after July, 1990, so about 150 patients were treated in GIVIO with pure L-form at a dose of 100 mg/m².

Information on toxic effects was obtained differently in the three trials. In NCIC-CTG patients were scored for toxic effects weekly during treatment and before each cycle, usually by oncology nurses or trial data managers. Full blood counts were also taken weekly, and biochemistry was done monthly before each cycle. In FFCD and GIVIO patients were assessed mainly by physicians, monthly, before each cycle. Full blood counts and biochemistry were also done monthly. In all trials the WHO toxicity scoring system was used.

	Total	Fluorouracil/ folinic acid	Control
Randomised	1526	754	772
Eligible*	1493 (97·8%)	736 (97·6%)	757 (98·1%)
Dukes' stage			
B, 0 positive nodes	841 (56·3%)	418 (56·8%)	423 (55·9%)
C, 1–4 positive nodes	494 (33·1%)	238 (32·3%)	256 (33·8%)
C, >4 positive nodes	144 (9·6%)	75 (10·2%)	69 (9·1%)
C, unknown number	14 (0·9%)	5 (0·7%)	9 (1·2%)
Location of primary tumour†			
Right colon	607 (40·7%)	311 (42·3%)	296 (39·1%)
Left colon	825 (55·3%)	395 (53·7%)	430 (56·8%)
Multiple	29 (1·9%)	15 (2 0%)	14 (1·8%)
Unknown	32 (2·1%)	15 (2·0%)	17 (2·2%)
Number (%) male	801 (53·7%)	388 (52·7%)	413 (54·6%)
Median age (range) in years	62 (19–86)	62 (19–78)	62 (26–86)

*% of randomised; all other percentages calculated over eligible patients. †Right colon=caecum, ascending, hepatic flexure and transverse; left colon=splenic flexure, descending sigmoid, and rectosigmoid junction.

Table 2: **Patients' characteristics by treatment group**

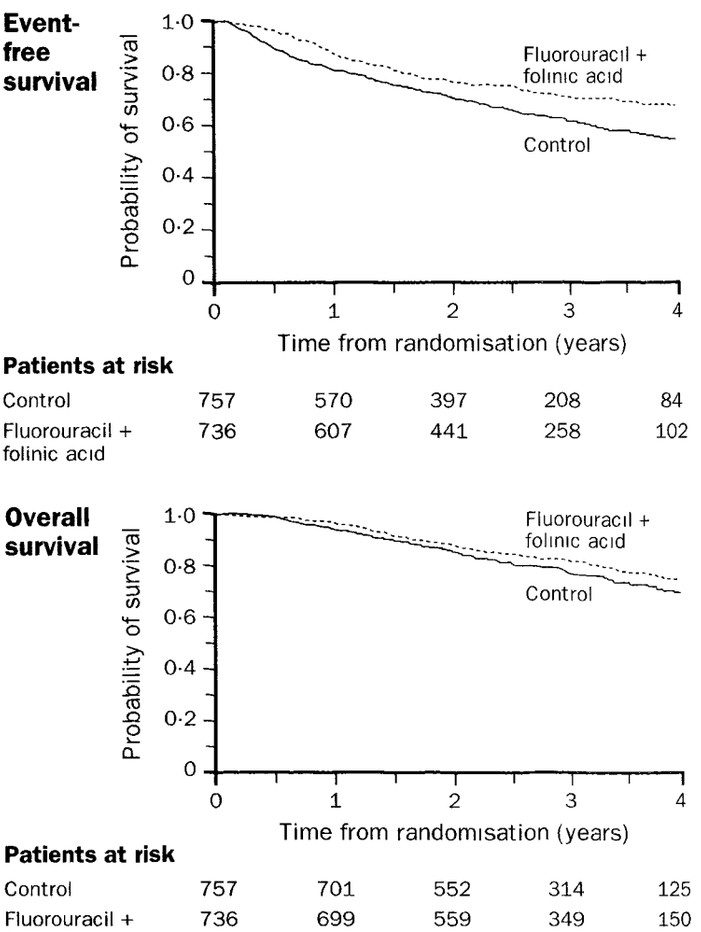


Figure 1: **Kaplan-Meier event-free and overall survival in treated and control groups**

	Stage B	Stage C	Total	p
3-year event-free survival (SE)				
Control	0 76 (0·04)	0·44 (0·06)	0·62 (0·03)	
Fluorouracil/folinic acid	0·79 (0 03)	0·62 (0·04)	0·71 (0·03)	
Hazard ratio for event-free survival (95% CI)*				
Unstratified	0·84 (0 62–1·12)	0·55 (0·44–0·70)	0·67 (0 56–0·80)	<0·0001
Stratified by country	0·84 (0·62–1·13)	0·55 (0·43–0·70)	0·67 (0·56–0·81)	<0·0001
Stratified by stage and country	· ·	· ·	0·65 (0 54–0·78)	<0·0001
3-year overall survival (SE)				
Control	0·90 (0·02)	0·64 (0 04)	0·78 (0·02)	
Fluorouracil/folinic acid	0·88 (0·02)	0·76 (0·03)	0·83 (0·02)	
Hazard ratio for overall survival (95% CI)*				
Unstratified	0 91 (0·63–1·34)	0·70 (0·53–0·92)	0·77 (0·62–0·96)	0·018
Stratified by country	0·93 (0·63–1·37)	0·71 (0·54–0·94)	0·79 (0·63–0·98)	0·034
Stratified by stage and country	· ·	· ·	0·78 (0·62–0·97)	0·029

*Fluorouracil/folinic acid *vs* control.

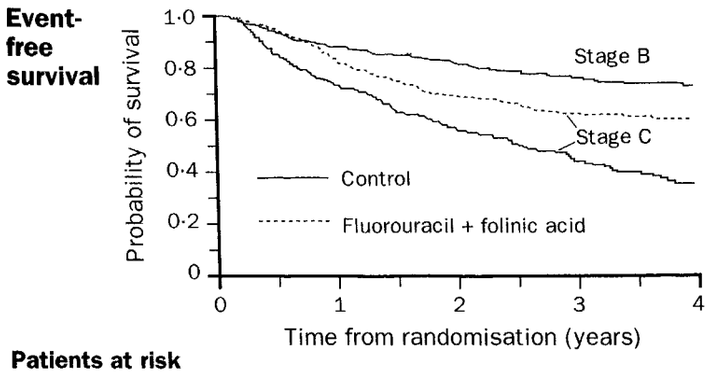
Table 3: **Event-free and overall survival**

Systems of quality assurance were similar in the three trials. In all three, consistency was checked and discrepancies from patients' notes were investigated.

Statistical analysis

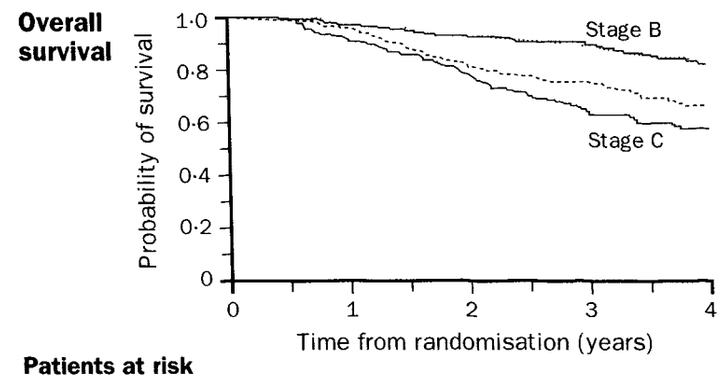
The study objective was to detect a 10% increase in overall survival associated with fluorouracil/folinic acid. This difference can be translated into a hazard ratio of 0·67, with the assumption of an exponential lifetime for patients and a 50% baseline survival rate. With these assumptions, the number of events required for 80% power with a conventional one-tailed test at 5%[13] was calculated. The number of events for the event-free survival comparison was achieved in November, 1992, and the number of deaths for the survival comparison a year later.

Event-free survival is defined as the time from randomisation to the first event. Events were first recurrence, second tumour, death with no relapse, or date of last observation. Survival is defined as the time from randomisation to death from any cause. All eligible patients were analysed on an intention-to-treat basis. Survival curves were generated by the Kaplan-Meier method. The cumulative frequency of relapses at various sites was also calculated.[14] The stratified log-rank test and Cox proportional hazards model were used to compare differences between treatment groups adjusted for prognostic factors. The 95% CI for the hazard ratios of treatment effect and other prognostic factors were determined from the asymptotic standard errors in the Cox regression model. Interaction terms for treatment by country and stage were tested under the final Cox model. The global test for interactions compared a model with main side-effects plus treatment by country and stage interaction to one with only main effects. A Cox regression model was used to assess prognostic factors other than country and stage; potential prognostic factors include site of primary colon cancer, age, number of positive nodes, and sex. All statistical tests reported are two-sided.



Patients at risk

Control, stage B	423	347	256	139	56
Fluorouracil/folinic acid, stage B	418	357	262	140	60
Control, stage C	334	223	141	69	28
Fluorouracil/folinic acid, stage C	318	250	179	118	42



Patients at risk

Control, stage B	423	403	327	189	72
Fluorouracil/folinic acid, stage B	418	399	328	188	87
Control, stage C	334	298	225	125	53
Fluorouracil/folinic acid, stage C	318	300	231	161	63

Figure 2: **Kaplan-Meier event-free and overall survival by Dukes' stage and treatment group**

	Event-free survival		Overall survival	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Treatment group				
Control*				
Fluorouracil/folinic acid	0·65 (0·54–0·78)	<0·0001	0·76 (0·61–0·96)	0·018
Age (years)				
≤65	NR			
>65		· ·	1·27 (1 01–1·59)	0·039
Stage				
B, 0 positive nodes*				
C, 1–4 positive nodes	2 01 (1·63–2·47)		2·17 (1·67–2·80)	
C, >4 positive nodes	4·05 (3·13–5·23)	<0·0001	5·40 (4·01–7·27)	<0·0001

*Reference category Not retained in final model (p>0·05).

Table 4: **Cox analysis of prognostic factors**

Results

Patients' characteristics

Of 1526 patients randomised, 1493 were confirmed as eligible. Reasons for ineligibility were incorrect histology (3), wrong stage (25), or other (5). The median follow-up times of the fluorouracil/folinic acid and control groups were 40 and 37 months (interquartile range [IQR] 29–48 for both groups), with 2% of patients censored alive with less than 1 year of observation. The last follow-up examination was between June and November, 1993. The cut-off date for analysis was Nov 1, 1993.

Characteristics of the patients are reported in table 2. A high proportion of stage B patients was observed, because recruitment of stage C patients was stopped prematurely in two trials when the fluorouracil/levamisole results became available.[5,6]

	Total (n=1493)	Fluorouracil/ folinic acid (n=736)	Control (n=757)
Site of relapse	394 (26·4%)	165 (22·4%)	229 (30·3%)
Liver	117 (7·8%)	39 (5·3%)	78 (10·3%)
Abdominal	80 (5·4%)	32 (4·3%)	48 (6·3%)
Extra-abdominal	79 (5·3%)	35 (4·8%)	44 (5 8%)
Multiple, unspecified	118 (7·9%)	59 (8·0%)	59 (7·8%)
Second tumour	35 (2·3%)	15 (2·0%)	20 (2·6%)
Death as first event			
Treatment related	1 (0·1%)	1 (0·1%)	·
Not related to tumour	25 (1·7%)	12 (1·6%)	13 (1·7%)
Total events	455 (30·5%)	193 (26·2%)	262 (34·6%)

Number (%) of patients in group.

Table 5: **Site of first event**

	GIVIO	NCIC-CTG	FFCD
Mucositis			
All grades	138 (38 5%)	146 (81·6%)	17 (14·4%)
≥grade 3	19 (5·3%)	37 (20·7%)	4 (3·4%)
Diarrhoea			
All grades	158 (44·1%)	141 (78·8%)	38 (32·2%)
≥grade 3	16 (4·5%)	47 (26·3%)	4 (3·4%)
Nausea and vomiting			
All grades	180 (50·3%)	121 (67·6%)	50 (42·4%)
≥grade 3	9 (2·5%)	18 (10·1%)	5 (4·2%)
Other toxic effects			
All grades	45 (12·6%)	117 (65·4%)	6 (5·1%)
≥grade 3	4 (1·1%)	16 (8·9%)	1 (0·8%)

Number (%) of patients; denominator=patients who received at least 1 cycle of treatment (358 GIVIO, 179 NCIC-CTG, 118 FFCD).

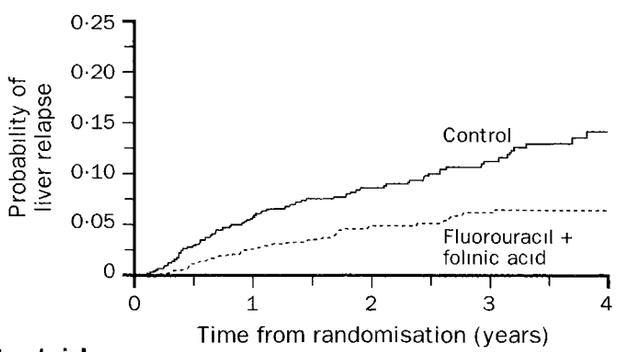
Table 6: **Non-haematological toxic effects**

Survival

Fluorouracil plus folinic acid significantly increased survival and event-free survival. There were 141 deaths in the treated group and 172 in the control group; 193 and 262 patients, respectively, experienced a relapse or a second tumour or death as a first event. Crude Kaplan-Meier event-free survival and survival curves are shown in figure 1. In both curves differences between treated and control patients were apparent by the first year. At 3 years, 83% of patients who had received fluorouracil/folinic acid and 78% of controls were alive, and 71% and 62%, respectively, were event-free.

Survival rates and hazard ratios are given in table 3. Results were consistent with and without stratification. The global test for interaction of treatment effect with stage and country was not significant for event-free (p=0·176) or overall survival (p=0·254). However, when only stage was taken into account the test was borderline significant for event-free survival (p=0·032). After adjustment, the fluorouracil/folinic group had significantly lower risks of an adverse event (35% lower) and death (22% lower) than the control group. Event-free and overall survival curves by stage and treatment are given in figure 2. The analysis including all 1526 randomised patients gave similar results.

In the multivariate Cox analyses nodal status was the only independent predictor other than treatment for overall or event-free survival, but age was significantly associated with survival (table 4). Sex and site of primary tumour were not significant. The risk of a negative event was two times greater in patients with 1–4 positive nodes than in stage B patients (no positive nodes); the risk was 4 times greater in patients with more than 4 nodes than in stage B patients.



Patients at risk

Control	757	570	397	208	84
Fluorouracil/ folinic acid	736	607	441	258	102

Figure 3: **Cumulative frequency of isolated liver relapse as first event**

First events

Overall there were 394 relapses. The pattern of relapse differed slightly between the treatment groups (χ^2 for heterogeneity=6·997, p=0·072). For hepatic recurrence as a first event (a third of all recurrences) the crude relapse rate was twice as high in the control group as in the fluorouracil/folinic acid group (table 5). The estimated cumulative frequency of isolated liver relapse at 3 years was 9% in the controls and 5% in the treated patients (figure 3). 35 patients developed a second tumour as the first event. Deaths unrelated to the tumour were equally distributed in the two groups.

Compliance with treatment was good. Information on compliance was available for 699 (92%) treated patients. The median number of courses received was 6 in all trials (IQR: GIVIO 6–6; NCIC-CTG 4–6; FFCD 6–6), and the median total fluorouracil dose delivered was 11·1 g/m² (10·7–11·1), 9·7 g/m² (7·4–11·0), and 12·0 g/m² (11·7-12·0), respectively.

The median relative dose intensity (dose intensity received/dose intensity planned) was 97% (90–100), 85% (76–96), and 98% (94–100), respectively. Weekly blood counts and relative dose reductions were done only in the NCIC-CTG trial. 43 patients (6%) never started treatment (2% NCIC-CTG, 7% GIVIO and FFCD). Overall, 94 patients (13%) did not complete protocol treatment in the absence of severe documented toxic effects.

Toxic effects

The commonest adverse effects of treatment were gastrointestinal (table 6). There was substantial variation among the trials (p value for association of side-effects with trial site <0·001). However, grade 4 gastrointestinal side effects occurred in fewer than 3% of patients in all trials. Toxic effects on bone marrow could not be fully documented in FFCD and GIVIO since blood counts were not monitored weekly. In GIVIO 41 of 358 evaluable patients had grade 1 or 2 leucopenia at 28 days. In FFCD there were 12 (of 118) cases of leucopenia grade 1 or 2. Neutropenia and thrombocytopenia occurred in 76% and 4%, respectively, of the NCIC-CTG patients. Grade 4 thrombocytopenia was not observed but 14% of evaluable patients had grade 4 neutropenia. There was only 1 episode of infection. This patient presented at hospital with febrile neutropenia 2 weeks after completing his first course of chemotherapy; he died of septic shock in the third week. He had had severe mucositis (grade 3) but this was resolving.

Discussion

This pooled analysis is the first to show a survival benefit in a direct comparison with surgery alone for colon cancer of a folinic-acid-modulated fluorouracil combination. The combination was well tolerated when given for 6 months at a good dose-intensity with no severe toxic effects.

Other adjuvant regimens are active in this disease.[3,5,15-17] MOF increased 5-year survival[3] but the benefit was no longer apparent at 8 years, perhaps because of the increased risk of secondary leukaemia and renal failure due to methyl-CCNU.[16] MOF was then compared with a folinic-acid-modulated fluorouracil regimen.[16] This regimen was administered intermittently for a year at almost twice the dose of fluorouracil that we used and three times the dose for folinic acid (cumulative calculated dose 18 g/m^2 for both drugs[16]). Fluorouracil plus levamisole is the most widely used adjuvant treatment in the USA and Canada in Dukes' stage C patients.[4,5] Treatment with levamisole alone had no detectable effect, but the combination with fluorouracil increased 3·5-year survival from 55% to 71%. The survival advantage remains significant at 5 years.[18] The role of levamisole remains unknown since the original trials did not have a group receiving fluorouracil alone.

Since the National Cancer Institute consensus conference in 1990, surgery alone is no longer deemed an ethical choice for Dukes' C patients in North America. According to the National Institutes of Health, fluorouracil plus levamisole is now the standard treatment for Dukes' C and high-risk Dukes' B patients, and levamisole has been approved by the Food and Drug Administration for this use.[19,20] Elsewhere, however, this combination is not considered standard treatment, and the question of whether adjuvant systemic therapy should be routinely given at all remains a matter of debate.[21] IMPACT adds some 1500 new cases in favour of chemotherapy. With IMPACT, there have been three published large-scale trials totalling more than 4000 randomised patients, showing a 20–30% reduction in mortality with post-surgical chemotherapy.[3,5] We believe there is now sufficient evidence to support the use of some form of adjuvant treatment in colon cancer.

Which adjuvant chemotherapy to use remains uncertain. MOF can be ruled out because this combination is less effective and has severe toxic effects and because methyl-CCNU is not available commercially. For patients with Dukes' C disease IMPACT has shown that a monthly regimen of high-dose folinic acid plus fluorouracil given for 6 months can achieve a similar survival benefit to that achieved with a year of therapy a different schedule of fluorouracil and folinic acid or with fluorouracil plus levamisole. At present there is no evidence that one regimen is better than the others. That will come from large-scale trials that are comparing fluorouracil and folinic acid regimens with fluorouracil/levamisole and exploring various high-dose/low-dose, short-term/long-term schedules of fluorouracil and folinic acid.

Another question is whether patients with stage B disease should be treated. We found a borderline significant interaction between stage and tretment for event-free survival but not for overall survival. An interaction suggests the possibility of a difference in the treatment effect by stage. The clinical question is whether this heterogeneity between stages is large enough to influence treatment choices. A different direction in the effect of treatment in node-positive and node-negative patients would definitely affect treatment decisions, but this is not the case for fluorouracil/folinic acid since there were fewer recurrences among treated patients of stage B or stage C. Although this evidence is consistent with the results of previous trials,[3,18] we believe that longer follow-up is needed for proper assessment of interaction between stage of treatment effect on survival. The results for fluorouracil/levamisole, which have longer follow-up, have been published only for the Dukes' C subset.

The IMPACT results are the first example of a prospective pooled analysis of cancer trials. The main benefit of data pooling was the acquisition of a sample of almost 1500 cases, which gave the analysis sufficient power to observe the estimated benefit in survival with median follow-up of 3 years. Another advantage of IMPACT is that the results are widely applicable. The absence of country/treatment interaction shows that the treatment regimen was used with reproducible efficacy by differently trained physicians, in different populations of patients, cared for under different health-care systems. Such treatment robustness is essential in clinical practice in oncology.

In conclusion, IMPACT confirms the efficacy of high-dose fluorouracil/folinic acid in Dukes' B and C patients and suggests that the antitumour activity obtained by the biochemical modulation of fluorouracil with folinic acid can be achieved with different schedules, dosages, and durations of treatment. The results also emphasise the need to reconsider the concept of standard therapy in this disease.

IMPACT study organisation

Steering and writing committee—R Labianca, S Marsoni, G Pancera, V Torri, A Zaniboni (GIVIO, Italy), C Erlichman, J Pater, L Shepherd, B Zee (NCIC-CTG, Canada), J F Seitz, C Milan, J P Pignon (FFCD, France).

Participants—Investigators who contributed to the design and management of the individual trials are indicated*.

GIVIO—E Aitini, G Apolone,* A Auzzani, S Banducci, S Barni, G D Beretta, O Biffi, F Bucci, G Cardi, D Cifatte, G Colucci, A Comandone, G Comella, C Confalonieri, A Confu, M Costanzo, C Crespi, E Damiani, D De Giorgi, V Dongiovanni, G Fabris, G Fabrizio, G Facendola, P A Fantoni, A Ferragni, B Fiori, F Florianello, L Frontini, E Galli, P Garattini, G Gherardi, A Giovanelli, F Guiliani, P Gosso, G P Janniello, B Kildani, S Leo, A Liberati,* G Maffione, E Maiello, L Maiorino, P Manente, G C Martignoni, M Marzola, M Mastrodonato, F Meriggi, B Molinari, G F Molinari, N Monferroni,* O Nascimben, C Natale, S Negretti, S Palazzo, D Panvini,* V Parisi, T Pedicini, F Peradotto, S Pessa, E Piatto, G Pizzi, A Prosperi, F Prusciano, C Rabbi, A Raina, A Ruggiero, C Sava, F Scanzi, P Setti Carraro, F Smerieri, B Stivala, A Taiana,* B Tardio, F Testore, A Tinazzi,* G Turcato, S Zonato.

NCIC-CGT—J Ayoub, K Belanger, G Biron, A J Bodurtha, G Boos, M Burnell, P Cano, D Charpentier, W S W Chow, J Chritchley, C Cripps, S P Dang, M L Davis, M Davidson, B Dingle, D Dryer, E Ferland, A Fields, S Fine, J Jolivet, L Kaiser, I Kerr, W I Kocha, C Kotwall, H Krieger, M Lepine-Martin, C Little, W S Lofters, M Maheu, M Moore, J Pater, B Pressnail, J Ragaz, H Rayner, R Reznick, T Ross, L Rotstein, L Rudinskas, B Schacter, A Shah, J Skillings, H Stern, M Tweeddale, T Vandenberg, D Walde, H J Watt, K Wilson A Wong, S Yoshida.

FFCD—C Baldit, J L Baroni, J P Bazin, L Bedenne,* A Blanchi, J C Bognel, J F Bosset, O Bouche, J M Brandone, R Bricot, P Burtin, L Cador, M Charbit, A Charlier, Y Courouble, P Couzigou, J Cuilleret, J R Delpero, M Ducreux, F Dumas, E Echinard, P L Etienne, J L Friguet, M Gignoux, M Giovannini,* J P Herr, J Lafon, P Letreut, J P Latrive, C Lauvaux, C Louvet, R Mackiewicz, C Maurel, C Messerschmitt, L Morand, J Moreau, T Morin, B Nordlinger, P M Noterdaeme, J C Ollier, R Picaud, P Peinkowski, J P Plachot, R Portet, H Rallier du Baty, P Rougier, G Rozental, B Sastre, J F Seitz, A Votte-Lambert, B Watrin, P Zeitoun.

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