Palliative and adjuvant chemotherapy in colorectal cancer

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Introduction

Colorectal cancer (CRC) is second in the league of cancer deaths in developed countries, for both men and women [1]. Twenty-five percent of new patients already have overt metastases at the time of presentation, and eventually 50% of newly diagnosed patients will succumb to metastatic disease. The presence of lymph node metastases and TNM stage remain the most important prognostic indicators, with adjuvant chemotherapy able to improve the survival of patients with curatively resected disease. The liver is the most frequent site of disease spread and two-thirds of patients with liver metastases have no evidence of extra hepatic disease [2]. However, surgical resection is only possible in 10% of patients with hepatic metastases.

Studies, in the early 1990s, in patients with advanced CRC indicated that the early administration of biomodulated 5-fluorouracil (5-FU) chemotherapy, initiated before the onset of symptoms, prolonged symptom-free survival (SFS), time to progression (TTP), and survival coupled with a good quality of life (QoL), when compared with patients where chemotherapy administration was delayed until the appearance of symptoms [3]. Around the same time, there was also the demonstration that systemic or hepatic artery infusion (HAI) therapy was able to increase overall survival, compared to best supportive care (BSC) [4,5]. The benefit of chemotherapy has also been demonstrated in elderly patients provided they are well enough to support the treatment (which can be given at reduced doses for the first cycles to test the tolerance). These observations, coupled with the recent progress made in terms of increases in response rate and survival with the new combination therapy regimens, confirm that systemic chemotherapy has a major role to play in the management of metastatic CRC.

At the same time, the efficacy of adjuvant chemotherapy following surgical resection of stage III colon cancer has been demonstrated using 5-FU and levamisole (LEV) in combination [6,7] and more recently using 5-FU-FA combinations [8,9].

In this review, we will discuss the place of chemotherapy in CRC but not its role in combination with radiotherapy in rectal cancer.

Palliative chemotherapy

5-Fluorouracil

5-FU has been used for the treatment of CRC for more than 30 years and during this time has been the subject of extensive research into the optimisation of its use. It is still used routinely, either alone or in combination, in the treatment of advanced CRC.

The early objective response rates (ORR) achieved with bolus 5-FU were around 10% and could be doubled either by combination with the biochemical modulators, leucovorin (folinic acid) or methotrexate (MTX) [10,11] (Table 1), or by administration as a protracted venous infusion. A meta-analysis of the six trials performed to compare the efficacy of bolus 5-FU versus continuous infusion (CI), showed 5-FU CI to be superior to 5-FU bolus in terms of objective response rate (ORR) (22% vs. 14%), and overall survival, with less grade 3 and 4 toxicities [12]. High doses of 5-FU and folinic acid (FA), given as a 48-hour continuous infusion, have also been shown to be efficient, and in a trial conducted by the Fondation Française de Cancérologie Digestive (FFCD) and Groupe d'Etude et de Recherche sur les cancers de l'Ovaire et Digestifs GERCOD, comparing this regimen with the monthly Mayo Clinic regimen (5 days bolus 5-FU and low-dose FA) resulted in a significant increase in ORR (33 vs. 14%, $P = 0.01$) and in progression-free survival (PFS) (6.5 vs. 5 months; $P = 0.012$) [13]. Over recent years, several other infusional regimens have been investigated. A high-dose, 24-hour, weekly, infusion of 5-FU (2.6 mg/m^2), modulated with high-dose FA (500 mg/m^2), has been developed by the German Arbeitsgemeinschaft Internistische Onkolo-

Table 1
Meta-analysis of trials of 5-FU modulation in colorectal cancer

Ref.	Treatment	No. patients	RR%	Survival
[10]	5-FU	1381	11%	11 months
			$P < 10^{-7}$	NS
	5-FU + FA		23%	11.5 months
[11]	5-FU	1178	10%	9.1 months
			$P < 0.0001$	$P = 0.024$
	5-FU + MTX		19%	10.7 months
[12]	5-FU bolus	1219	14%	11.3 months
			$P = 0.0002$	$P = 0.04$
	5-FU CP		22%	12.1 months
[21]	5-FU			
			NS	NS
	5-FU + IFN	17 trials		
	5-FU + FA		18%	$P = 0.07$ in favour of 5-FU + FA
		3690	$P = 0.012$	
	5-FU + IFN		23%	
	5-FU + FA	patients		
			NS	NS
	5-FU + FA + IFN			
[82]	IVC	391	14%	12.2 months
			$P < 10^{-10}$	NS
	HAI		41%	16 months
[82]	BSC or bolus i.v. 5FU	263	–	10.1 months
				$P = 0.0009$
	HAI		–	14.5 months

5-FU: 5-Fluorouracil; FA: Folinic acid; MTX: Methotrexate; IFN: interferon; CP: continuous perfusion; HAI: intra-arterial hepatic chemotherapy; IVC: intravenous chemotherapy; BSC: best supportive care; i.v.: intravenous; RR: response rate; NS: non significant.

gie (AIO) [14]. The European Organization for Research and Treatment of Cancer (EORTC)–Gastro Intestinal Tract Cancer Cooperative Group (GITCCG) comparing this regimen with the Mayo-Clinic regimen (5 days high-dose 5-FU and low-dose FA), reported a non-significant increase in the response rate (RR) (20 vs. 11%) and a slight, but significant, increase in the PFS (4 to 6.4 months; $P = 0.02$) [15]. Similar data have been reported by the Spanish Cooperative Group using a 48-hour weekly infusion of 5-FU [16]. In many European countries, infusional regimens are now the therapy of choice. However, currently the choice of one particular infusional regimen over another is based more on national preferences than on sound scientific data [17].

Other possibilities that have been investigated in an attempt to optimise the efficacy of 5-FU therapy, and those that have demonstrated some kind of benefit in terms of RR or tolerance, have included 'schedule-specific biomodulation' [18], 5-FU chronomodulation [19] and pharmacokinetic monitoring of the 5-FU dose [20]. In contrast, no benefit was observed when interferon was combined with 5-FU with or without FA [21] (Table 1).

Oral 5-FU pro-drugs

Through the years many attempts to develop oral 5-FU have been made. These products are more convenient and maybe somewhat less toxic than the bolus 5-FU-FA regimens, and presently two drugs, capecitabine (Xeloda^{R}) [22,23] and UFT (a combination of tegafur and uracil) [24,25] have demonstrated in phase III studies activity equivalent to bolus 5-FU-FA in terms of survival, with a slight advantage in ORR for capecitabine (Table 2). However, no comparison of these oral 5-FU prodrugs with the infusional regimens of 5-FU that are, very popular in Europe has been done. Capecitabine has been approved in Europe for the first-line treatment of CRC.

New agents and 5-FU-based combination therapy

The future for 5-FU-based therapy, however, lies in its combination with other, newer agents with non-overlapping mechanisms of action. Several new agents have demonstrated at least similar efficacy to 5-FU in the second-line treatment of advanced CRC

Table 2
Randomised trial testing new oral 5-FU prodrugs: UFT and Capecitabine versus FU-FA Mayo Clinic regimen in patients with metastatic colorectal cancers

Ref.	Protocol	No. patients	%OR	Time to progression	Survival
[24]	FU-FA Mayo Clinic	816	15% NS	? 	? NS
	UFT + FA		12%	?	?
[25]	5-FU-FA Mayo Clinic	380	9% NS	3.3 months NS	11.9 months NS
	UFT + FA		11%	3.4 months	12.2 months
[23]	5-FU-FA Mayo Clinic	605	15.5% $P = 0.005$	4.7 months NS	13.3 months NS
	Capecitabine		24.8%	4.3 months	12.5 months
[22]	5-FU-FA Mayo Clinic	602	17.9% $P = 0.013$	4.8 months NS	13.1 months[a] NS
	Capecitabine		26.6%	5.3 months	14 months[a]

FU-FA: 5-FU modulated by folinic acid, UFT: combination of tegafur/uracil; NS: non-significant; OR: objective response.
[a] Given during the oral presentation at American Society of Clinical Oncologists (ASCO) meeting 1999.

in patients relapsing on, or refractory to, 5-FU-based first-line therapy. These agents include CPT-11 [26] and oxaliplatin [27].

CPT-11

Second-line. CPT-11, is a potent inhibitor of topoisomerase I and exerts its cytotoxicity through inhibition of DNA replication. In phase II/III studies, CPT-11 has demonstrated consistent objective anti-tumour activity in the second-line treatment, in patients with 5-FU-resistant metastatic CRC, with response rates in the range 11 to 23% [26], and a significant survival advantage, with a better quality of life in two large phase III studies, comparing CPT-11 to BSC [28] or infusional 5-FU regimens [29]. Thus, CPT-11 confers a clear clinical benefit to patients who have failed on standard 5-FU therapy, and CPT-11 is considered to be more clinically effective and cost-effective [30], than CI 5-FU following failure on previous 5-FU-FA regimens.

First-line. CPT-11 has also demonstrated first-line, single-agent activity in the treatment of patients with advanced metastatic CRC [31–33]. The collective data from two US phase II trials yielded a confirmed RR of 29.2%, a median TTP of 4.2 months and a median survival of 11.4 months [31,32]. A European phase II trial yielded a RR of 18%, a median TTP of 4.2 months and a median survival of 14.7 months [33], confirming the activity of irinotecan in this clinical setting.

CPT-11's novel mechanism of action and its activity, logically led to its development as a component of first-line therapy for advanced CRC and its combination with 5-FU-based regimens. Phase I dose-escalation studies of CPT-11 in combination with both bolus and infusional 5-FU-FA regimens, identified suitable dosing regimens for phase II and III studies in the US and Europe [34,35]. In the US, a dose escalation and pharmacokinetic study of a CPT-11/5-FU-FA bolus regimen provided the recommended dosing schedule for a pivotal US phase III trial [34]. In Europe, two phase I trials of CPT-11 in combination with two different 5-FU-FA infusional regimens, the de Gramont [35] and German AIO regimens [36], formed the basis of the infusional 5-FU-FA regimens used in the pivotal European phase III study [37]. Two, European and US, phase III trials have been conducted, and the inclusion and exclusion criteria for patients were similar [37,38]. In the European trial [37], a total of 387 patients were allocated to one of two infusional 5-FU-FA treatment regimens (AIO or de Gramont), depending on the preference of the particular study centre, and then randomised within each study centre to the regimen of choice plus or minus CPT-11. In the US trial of Saltz et al. [38], a total of 683 patients were allocated to receive one of three different regimens, either CPT-11 alone, bolus 5-FU-FA alone or CPT-11 plus bolus 5-FU-FA in combination. In the European trial, the results demonstrated a significant advantage in favour of the CPT-11 arm. The median TTP in this study was 6.7 versus 4.4 months, the median time to treatment failure (TTF) was 5.3 versus 3.8 months, the confirmed objective tumour RR was 35% versus 22% and the median survival 17.4 versus 14.1 months for the CPT-11/5-FU-FA and 5-FU-FA arms, respectively (Table 3). The median duration of

Table 3
Randomised trials testing the efficacy of CPT-11 and oxaliplatin in combination with 5-FU-FA in metastatic colorectal patients

Ref.	Protocol	No. evaluable patients	ORR	Time to progression	Survival
[19]	5-FU-FA chrono	100	16% $P < 0.001$	6.1 months $P = 0.048$	19.4 months NS
	Idem + oxaliplatin	100	53%	8.7 months	19.9 months
[46]	LV5-FU2	210	22% $P = 0.0001$	6.2 months $P = 0.0003$	14.7 months $P = 0.12$
	Idem + oxaliplatin	210	51%	9 months	16.2 months
[37]	LV5-FU2 or weekly 5-FU-FA	187	22% $P < 0.005$	4.4 months $P < 0.001$	14.1 months $P = 0.031$
	Idem + CPT-11	198	35%	6.7 months	17.4 months
[38]	5-FU-FA Mayo Clinic	226	21%	4.3 months	12.6 months
	CPT-11 alone	231	–	–	–
	5-FU + FA + CPT-11 weekly	223	39%	7 months $P = 0.004$	14.8 months $P = 0.097$

ORR: overall response rate; 5-FU-FA: 5-FU modulated by folinic acid; chrono: chronomdulated administration; LV5-FU2: de Gramont regimen; NS: non-significant; Idem: the same.

response was 9.3 versus 8.8 months for the two treatment arms. In the US trial, the median TTP was 7.0 versus 4.3 months, the confirmed objective tumour RR was 39% versus 21% and the median survival 14.8 versus 12.6 months, for the CPT-11/5-FU-FA versus 5-FU-FA arms, respectively (Table 3). The responses for the CPT-11 alone arm were very similar to those for the 5-FU-FA arm [38].

The efficacy results for these two studies were remarkably similar with a significant improvement in TTP, TTF, and ORRs in the CPT-11 combination arms in both studies. The most significant finding of both studies was that the combination of CPT-11/5-FU-FA provided a statistically significant survival advantage. This was even though 59% and 70% of the control 5-FU-FA patients versus 41% and 52% in the CPT-11/5-FU/FA arm, went on to receive second-line therapy in the European and US trials, respectively. These studies clearly demonstrated that CPT-11 in combination with 5-FU-FA, as first-line therapy, improved tumour control compared to 5-FU-FA irrespective of the mode of 5-FU-FA administration. The side-effects of the combination, were manageable, non-cumulative and reversible. As a result, the addition of CPT-11 to a weekly or biweekly infusional 5-FU-FA regimens has been recommended as the reference regimen for the first-line treatment of metastatic CRC and CPT-11 in combination with both a bolus and an infusional 5-FU-FA regimen was approved by the Food and Drug Administration (FDA), in April 2000, for the first-line treatment of metastatic CRC.

New combinations will be developed in the future and a RR of 42% with median response duration of 6.5 months has been reported when CPT-11 has been used in combination with oxaliplatin plus granulocyte colony-stimulating factor (G-CSF) support [39]. 5-FU high dose folinic acid and mitomycin C (MMC) is an effective second-line therapy [40]. A randomised study of CPT-11/MMC versus oxaliplatin/MMC in patients failing on 5-FU-based therapy yielded RRs of 21% and 16% respectively, with CPT-11/MMC being slightly superior to oxaliplatin/MMC in terms of median time to disease progression [41].

Oxaliplatin

Second-line. Oxaliplatin (LOHP) is a third-generation platinum compound. When used as a single agent, oxaliplatin has achieved response rates of around 10% in patients with metastatic CRC previously treated with 5-FU [42,43].

First-line. Oxaliplatin has seldomly been used as a single agent, however in a prospective phase II trial an ORR of 24% has been achieved in patients with previously untreated metastatic CRC with peripheral cumulative neurotoxicity as the main dose-limiting toxicity (DLT) [44]. Combination of oxaliplatin with 5-FU-FA, has been demonstrated in vitro to be synergistic, and this combination used as either a three-drug chronomodulated regimen or as standard flat infusions of oxaliplatin and 5-FU-FA, has resulted in response rates of around 58% in pre-treated patients [45]. A recent phase III study of the addition of oxaliplatin to chronomodulated 5-FU-FA for the first-line treatment of metastatic CRC showed oxaliplatin to significantly improve the response rate (53% vs. 16%) and the PFS (8.7 vs. 6.1 months;

$P = 0.048$), but with no change in median survival (19.9 vs. 19.4 months) [19]. However, most of the patients in the control arm crossed towards the chronomodulated oxaliplatin 5-FU-FA combination at progression and this might explain both the long median survival reported in the two groups and the absence of a survival difference (Table 3) [19,45]. Combined oxaliplatin and chronomodulated 5-FU-FA displayed acceptable toxicity, with diarrhoea the most frequent acute side-effect. In a second randomised trial not using chronotherapy, but the de Gramont schedule with or without oxaliplatin at a dose of 85 mg/m^2, every 2 weeks (LV5-FU2-LOHP or FOLFOX4 regimen), a significant advantage in favour of the FOLFOX4 arm has been reported for both the RR (51% vs. 22%; $P = 0.0001$) and the progression-free survival (PFS) (median: 9 months vs. 6.2 months; $P = 0.0003$), but the difference for the overall survival was non significant (16.2 months vs. 14.7 months; $P = 0.12$) (Table 3) [46]. However, in a multivariate analysis conducted on this study [47], in addition to good performance score (PS) and normal alkaline phosphatase level, the FOLFOX4 regimen was a significant favourable prognostic factor for survival, and this regimen is one of the first-line therapies commonly used in some European countries.

For patients resistant to 5-FU-FA, oxaliplatin in combination with 5-FU-FA (FOLFOX) has been shown to be an effective regimen in a large prospective international trial in which oxaliplatin was added to the same 5-FU-FA regimen used as first-line treatment with an ORR of 11% and a median duration of tumour growth control (TGC) of 4 months [48]. Oxaliplatin dose intensification studies of (100 mg/m^2 every 2 weeks) in combination with the bimonthly de Gramont infusional FOLFOX6 regimen, in pre-treated patients, have shown oxaliplatin dose intensification to yield increased RR and PFS in this situation [49]. These data are also supported by the data obtained from the extensive compassionate use programme [50].

CPT-11-oxaliplatin combination. CPT-11 is also being investigated in second-line therapy in combination with oxaliplatin in patients with advanced CRC both in terms of safety and pharmacokinetics [51,52]. CPT-11 in combination with oxaliplatin has also been compared for efficacy and toxicity with an alternating combination of CPT-11/5-FU-FA and oxaliplatin/5-FU-FA [53]. The CPT-11/oxaliplatin combination showed encouraging results both in terms of RR and TTP, and studies of the combination with and without 5-FU-FA are ongoing [53,54]. A multicentric randomised phase II trial of CPT-11/5-FU-FA versus oxaliplatin/5-FU-FA versus CPT-11/oxaliplatin, in patients who have failed on previous 5-FU-FA therapy, has just been completed [55]. It has been reported that after external evaluation and review of responses, similar results for all 3 combinations with respectively ORRs of 12.1%, 22.6% and 16.7%, tumour growth control (PR and SD) in 64%, 74% and 67% of patients, median duration of response of 8.0, 6.7 and 6.5 months and overall survivals of 12.2, 11.5 and 11 months. These data illustrate that none of these regimens reached the 40% ORR claimed in other unicentric trials, but that with combined second-line chemotherapy regimens a median survival of one year may be expected.

Management of systemic chemotherapy in metastatic CRC

From the reported experiences described above, it is clear that CPT-11 and oxaliplatin in combination with 5-FU-FA are the most promising second-line and even third-line therapies, following failure of 5-FU-based therapy, for patients with advanced CRC. The main problem presently is the choice that has to be made between 5-FU-FA regimens and polychemotherapy as first-line therapy, which depends on patient demand, prognostic factors such as the extent of tumour spread, PS, age, white blood cell count (WBC), haemoglobin, lactate dehydrogenase (LDH) etc., and in the case of 5-FU-FA, the possibility to use active second- and even third-line chemotherapy regimens. Only prospective trials will be able to help us in this choice coupled with the development of our knowledge of new biological factors that might allow us in the future to select the best chemotherapy regimen for each patient.

Tailoring therapy to patients with hepatic metastases

Therapy can also be specifically tailored for patients with hepatic metastases. As stated previously, approximately 50% of patients with CRC will develop liver metastases and of these, two thirds will have no evidence of extra hepatic disease. Hepatic surgery is the only chance of curative treatment in these patients with a five-year survival rate of between 25 and 45% when metastases are resectable and isolated [56]. Therapy can also be administered by HAI after resection to improve outcome [57].

For patients with non-resectable hepatic metastases, HAI with the administration of 5-FU or floxuzidine (FUDR) was explored in the 1980s and demonstrated a consistent benefit in terms of RR, and some-

times survival, when compared with systemic 5-FU treatment alone, especially when performed in experienced centres in patients with good PS, liver involvement of less than 50%, an absence of extrahepatic disease and CEA levels under 100 ng/ml [5,56,58,59] (Table 1). Its use, however, has been limited by the local toxicity of FUDR, the technical skill required, the development of extra-hepatic metastases and the recent demonstration of more active systemic chemotherapies. However, the use of HAI is not dead, even if its indications are rare (5–10% of liver metastasis) and more innovative regimens are presently being tested such as the combination of systemic CPT-11/5-FU-FA with HAI of pirarubicin [60], which facilitated hepatic resection in 2 out of 18 patients. Single-agent systemic CPT-11 in combination with localised HAI floxuridine and dexamethasone [61] has been shown to be safe and effective.

On the topic of isolated unresectable liver metastases, strategies have been developed over several years, which use chemotherapy as a means of reducing the tumour bulk, rendering previously non-resectable liver metastases resectable. This has been suggested by a single institution retrospective study using chronomodulated oxaliplatin combined with 5-FU-FA in a large population of selected patients for whom chemotherapy has facilitated secondary resections in 16% of patients with initially non-resectable hepatic metastases [62]. This has also been reported for other chemotherapy regimens and is presently being explored in a prospective trial of patients with strict criteria for non-resectability using the tritherapy 5-FU-CPT-11-LOHP.

Adjuvant chemotherapy

As stated in the introduction to this review, 25% of patients with colorectal cancer present with overt metastases, but, significantly, eventually 50% of newly diagnosed patients will succumb to metastatic disease. This means that approximately 25% of patients must have microscopic metastatic disease at the time of surgical resection.

Systemic chemotherapy

Adjuvant, systemic, 5-FU plus LEV chemotherapy for patients with curatively resected stage III colon cancer was shown, in an early intergroup study in the US [6], to produce a 3-year recurrence and survival advantage over surgery alone. The risk of recurrence was reduced by 41% ($P =< 0.0001$) and overall survival improved by 33% ($P \sim 0.006$). These benefits were still observed during long-term follow-up [7]. Subsequently, adjuvant 5-FU-FA therapy was tested, using different treatment schedules, in 4 randomised trials. The pooled data from three multicentre trials from Italy, Canada and France using the same treatment regimen, showed adjuvant 5-FU (370–400 mg/m^2) plus high-dose FA (200 mg/m^2) daily for 5 days, beginning 4 weeks post surgery and then administered every 4 weeks for six cycles, to confer a significant 3-year recurrence-free survival and overall survival advantage over surgery alone in patients with Dukes' B and C disease [8]. These results were confirmed by a study from the Mayo Clinic [9]. Several studies comparing adjuvant 5-FU/LEV adjuvant therapy with 5-FU-FA adjuvant therapy in patients with stage II and III disease have shown that 6 months of 5-FU-FA was at least as effective as 12 months 5-FU/LEV in stage III (Dukes' C) patients [63–67]. After which 5-FU-FA was considered the new standard adjuvant treatment for stage III colon cancer (Table 4). In a prospective randomised trial of the double modulation of 5-FU by LEV plus FA [64], 6 months treatment with 5-FU/LEV/FA was superior to 12 months treatment with 5-FU/LEV. Similarly, a US NSABP trial, in which patients were randomised to receive 5-FU-FA, 5-FU/LEV or 5-FU/LEV/FA, showed a prolongation of DFS that favoured the 5-FU-FA group over 5-FU/LEV (65% vs. 60%; $P = 0.04$), and a prolongation of overall survival that was of borderline significance [65]. However, the UK QUASAR study conducted on approximately 5000 patients [66] has demonstrated the superiority of adjuvant 5-FU-FA over 5-FU-LEV-FA in terms of survival (Table 4). The QUASAR study also demonstrated that there was no difference between high- and low-dose FA regimens and no apparent difference between weekly or monthly regimens of 5-FU-FA.

Presently, new trials are evaluating the optimised 5-FU-FA regimens (de Gramont, AIO etc.) with 24- or 48-hour infusions. The GERCOD trial, closed after the inclusion of 900 patients, reported preliminary results demonstrating that the bimonthly infusional 5-FU-FA regimen was better tolerated than the monthly Mayo Clinic regimen [67]. One large European trial (PETACC-2) compares the infusional 5-FU-FA regimens (de Gramont and AIO) to the monthly Mayo Clinic bolus 5-FU-FA regimen. This trial aims to recruit 1800 patients and will be powerful enough to demonstrate even a small increase in overall survival. Two trials have tested the use of i.v. continuous infusion (Lokich regimen). One study from the UK compared the Lokich regimen for 3 months to the Mayo Clinic 5-FU-FA regimen for 6

Table 4
Comparative trials of 5-FU-levamisole (LEV) and 5FU-FA combinations for adjuvant treatments in colon cancer (stage II and III)

Studies	No. patients (% stage II)	Protocol	Recurrence-free survival	Overall survival
QUASAR-1 [66]	4947	5-FU-high-dose FA + placebo		
			65.1%	71.5%
		5-FU-low-dose FA + placebo		
			$P = 0.016$	$P = 0.06$
		5-FU-high-dose FA + LEV		
			63%	69.4%
		5-FU-low-dose FA + LEV		
NSABP C04 [65]	2151	5-FU-LEV (1 year)	60%	70%
			$P = 0.04$	$P = 0.07$
	(41%)	5-FU-FA weekly (8 months)[a]	65%	74%
		5-FU-FA weekly (8 months) + LEV		
INT 0089 [63]	3759	5-FU-LEV (1 year)	58%[c]	67%
			NS	NS
	(20%)	5-FU-FA weekly (8 months)[a]	62%	70%
			NS	NS
		5-FU-FA Mayo (6 months)[b]	63%[c]	71%
			$P = 0.05$	NS
		5-FU-FA Mayo + LEV (6 months)	63%	73%
			NS	NS

[a]5-FU-FA weekly: 5-FU: 500 mg/m^2 + FA: 500 mg/m^2, weekly for 6 weeks + 2 weeks rest.
[b]5-FU-FA Mayo: Mayo Clinic regimen: 5-FU: 425 mg/m^2 + FA: 20 mg/m^2, 5 days every 4 weeks and 5 weeks after cycle 3).
[c] At 5 years for National Surgical Adjuvant Breast and Bowel Project (NSABP) C04, at 4 years for INT 0089, at 4 years for NCCTG-NCIC trial.
Analysis 2 by 2: survival for 5-FU-FA group (6 months) > survival 5-FU-LEV (6 months): $P = 0.005$.
NS: non-significant.

months [68], in 716 patients with stage II or III colon or rectal cancer; no difference in overall survival was reported and the 5-year disease-free survival was increased in the Lokich regimen arm (69% vs. 60%; $P = 0.01$) in patients with stage II and III colon and rectal cancer. The Lokich regimen was also associated with less toxicity. In the second US intergroup study [69], 1078 stage II and III colon cancer patients were randomised between the i.v. 5-FU continuous infusion (using a lower dose of 5-FU) and the Mayo Clinic regimen plus LEV. In this trial, there was no difference in the 3-year survival between the two groups, but an increase in grade 4 toxicity was seen in the Mayo Clinic regimen arm, contrasting with twice as many patients stopping their treatment in the i.v. continuous infusion arm.

In conclusion is now generally agreed that in patients with lymph node metastases (UICC stage III/Dukes' C), post-operative adjuvant therapy for 6 months, with a 5-FU-FA regimen, reduces recurrence and increases survival [6–9]. However, clinicians remain less convinced by the evidence for a role for adjuvant therapy in the treatment of stage II disease, the group to which the remaining 25% of patients who subsequently progress to metastatic disease belong. Table 5 shows that, in a meta-analysis of all the trials that tested adjuvant 5-FU-FA versus control, there is an excellent 5 year survival (82% vs. 80%) and no significant benefit in favour of 5-FU-FA [70]. However, the analysis reported by the NSABP tends to support a similar relative effect of adjuvant chemotherapy in stage II and in stage III [71]. As a result, treatment policies vary widely across Europe and the US for patients with this disease stage.

Raltitrexed (Tomudex^R) which is a pure TS inhibitor has been evaluated versus 5-FU-FA in the PETACC 1 trial which has been prematurely closed, after the randomisation of 1800 patients, because of toxicity. Oral 5-FU prodrugs, like UFT, have demonstrated some efficacy in Japanese trials and is currently being tested in the NSABP CO6 trial,

Table 5
Efficacy of adjuvant chemotherapy with 5-FU-FA regimens in stage II colon cancer: results of the meta-analysis IMPACT B2 [70]

5-year survival	5-FU-FA (%)	Control (%)	*P* (unilateral)
Event-free	76	73	0.061 (0.137[a])
Overall	82	80	0.057 (0.130[a])

[a] after adjustment for age and differentiation.

while capecitabine is being tested in an ongoing trial (Roche trial).

CPT-11 and oxaliplatin, the two newer drugs active in the treatment of CRC, have both demonstrated their efficacy in the treatment of advanced colorectal cancer and are being evaluated in an adjuvant setting. Presently, there are at least 5 randomised studies of CPT-11 in combination with 5-FU-FA for the treatment of CRC in an adjuvant setting underway, in the US and Europe (Table 6). The objectives of these studies are to evaluate overall survival and disease-free survival (DFS) and to prospectively evaluate prognostic markers such as *thymidylate synthase*, *TP53*, *p21*, *p27*, *VEGF*, *DCC* gene changes, microsatellite instability and topoisomerase 1 levels. One study is ongoing in rectal cancer patients (Table 6).

In the case of oxaliplatin, there are at least 2 randomised adjuvant trials in stage II–III colon cancers that are ongoing, one in Europe (MOSAIQ) and the other in the US (NSABP). There are also ongoing studies on the efficacy of combination of oxaliplatin, 5-FU-FA and radiotherapy in advanced rectal cancer.

For resectable liver metastases, neoadjuvant chemotherapy is also presently being investigated in an intergroup multicentric trial conducted by the EORTC-GITCCG (40983), where patients are randomised between immediate resection of their metastases, and 6 cycles of FOLFOX4 before, and in case of efficacy, after resection of their metastases.

Future adjuvant studies with CPT-11 and oxaliplatin are likely to include combinations with oral fluoropyrimidines, because of the recent approval in Europe of capecitabine (Xeloda) and UFT for first-line therapy. Also, the issues surrounding the role of adjuvant therapy in stage II disease still need to be resolved, and more adjuvant studies in this patient population are required.

The demonstrated efficacy of i.v. chemotherapy explains why targeted chemotherapy approaches appear less interesting. The ongoing investigations of intraportal (IporC) and intraperitoneal (IperC) chemotherapy and immunotherapy are presented below.

Local chemotherapy

The local administration of adjuvant chemotherapy is supported by the fact that the portal and peritoneal routes are the main routes for the dissemination of tumour cells in patients with CRC. The first studies of local chemotherapy were empirical, especially where the intraoperative intraluminal administration of chemotherapy was concerned [72]. IperC was also investigated, but has never been extensively studied.

Intraperitoneal chemotherapy

The intraperitoneal administration of chemotherapy results in an important increase in the concentration of 5-FU at the peritoneal surface and, to a lesser extent, in the portal blood (60% increase) compared to i.v. administration. Only a few clinical trials have been reported on the efficacy of IperC. One randomized study conducted on 66 patients at very high risk of recurrence has compared i.v. 5-FU versus IperC and demonstrated a significant reduction in the rate of peritoneal recurrence (2/10 vs. 10/11; $P = 0.003$); however there was no reduction in the number of liver metastases and no improvement in the overall survival [73]. A second study [74] on 267 patients demonstrated that IperC was safe and feasible and reported limited efficacy, with a non-significant increase in overall survival (74% vs. 69%) for the entire group, but a significant increase in DFS for patients with stage II colon cancer (89% vs. 73%). The power of this study was limited because of the small patient number and complementary studies are needed.

Two other studies have explored the efficacy of IperC combined with i.v. chemotherapy. The first was a comparison of i.v. 5-FU-FA administered 4 days every 4 weeks combined with IperC using 5-FU-FA for 2 days every 4 weeks versus surgery alone [75] in 121 stage II and III patients. A significant survival advantage in favour of the combined chemotherapy arm (78% vs. 63% at 5 years; $P = 0.05$) was reported together with a significant reduction in the rate of hepatic and peritoneal recurrences. In the second trial, in 236 patients, the same combined IperC and i.v. chemotherapy was compared with a 1-year treatment with 5-FU-LEV [76]. After a median follow-up of 27 months, there was a significant reduction in the recurrence rate in the investigational arm (17/94 vs. 35/96; $P = 0.0015$) and a better tolerance.

These studies suggest some kind of efficacy for IperC. However, they provide no indication of its relative value compared to 6 months of i.v. 5-FU-FA, which presently is the recommended adjuvant treatment for stage III colon cancer. The results of the FFCD 9204-EORTC 40911 randomised trial (Table 6) in which approximately 400 patients who have received an IperC therapy combination are to be compared with patients receiving i.v. chemotherapy alone, will tell us if this combination needs to be studied further.

Intraportal chemotherapy

Postoperative IporC aims to destroy tumour cells, which have migrated into the liver through the portal vein. Adjuvant IporC using 5-FU with or without

Table 6
Summary of some of the ongoing and planned adjuvant therapy trials in the US and Europe in Stage II and III colon cancers

Trial	Planned accrual	Accrual 03/01	Stage	Regimen
US intergroup study CLB-89803	1260	700	Stage III colon Stratified: (i) lymph nodes (ii) histology. (iii) CEA	*Arm 1.* Bolus 5-FU (500 mg/m^2)–FA (500 mg/m^2) weekly ×6, q8wk *Arm 2.* idem plus CPT-11: 125 mg/m^2 weekly ×6, q8wk
157-001 America	1800		Stage III colon	*Arm 1.* 5-FU-FA bolus plus edrecolomab *Arm 2.* 5-FU-FA alone
157-002 Rest of the World	2700	1435	Stage III colon	*Arm 1.* 5-FU-FA plus edrecolomab *Arm 2.* 5-FU-FA alone bolus *Arm 3.* Edrecolomab alone
CLB-9581	–	–	Stage II	*Arm 1.* Surgery alone *Arm 2.* Surgery plus edrecolomab
EST 1290			Stage III	*Arm 1.* 5-FU/LEV *Arm 2.* Autologous tumour cell vaccine *Arm 3.* 5-FU/LEV + Autologous tumour cell vaccine
			Stage II	*Arm 1.* Autologous tumour cell vaccine *Arm 2.* Control
European EORTC 40911-FFCD 9204			Stage II and III	*Arm 1.* 5-FU/LEV *Arm 2.* 5-FU/LEV + IperC or IporC *Arm 3.* 5-FU-FA *Arm 4.* 5-FU-FA + IperC or IporC
GISCAD + GOIRC (Italy)			Stage II and III	*Arm 1.* 5-FU-FA *Arm 2.* IporC *Arm 3.* 5-FU-FA + IporC
V307 PETACC 3	1800	400	Stage III colon (and stage II)	*Arm 1.* De Gramont or AIO regimens[a] *Arm 2.* De Gramont or AIO regimens[a] plus CPT-11: 80 mg/m^2 (weekly) or 180 mg/m^2 (2-weekly)
ACCORD-2 FFCD	400	190	High risk stage III colon	*Arm 1.* De Gramont *Arm 2.* De Gramont plus CPT-11: 180 mg/m^2 (2-weekly)
AERO R-98	600	60	Stage II and III rectal cancer	*Arm 1.* 5-FU-FA Mayo or LV5-FU2 *Arm 2.* Idem plus CPT-11 180 mg/m^2
PETACC 4	1960	0	Stage II Colon	*Arm 1.* Surgery alone *Arm 2.* Surgery plus de Gramont or AIO regimens plus CPT-11
QUASAR-2	4000	0	Stage III colon	*Arm 1.* CPT-11 plus bolus 5-FU-FA *Arm 2.* CPT-11 plus capecitabine

[a] de Gramont regimen = 200 mg/m^2 FA iv for 2 hours and 400 mg/m^2 5-FU bolus followed by 600 mg/m^2 5-FU iv over 22 hours days 1 and 2 every 2 weeks; AIO = 500 mg/m^2 FA with 2.6 g/m^2 5-FU iv administered over 24 hours every week. IporC = intraportal chemotherapy; IperC = intraperitoneal chemotherapy; i.v. = intravenous; q = every; wk = week; EORTC = European Organization for Research and Treatment of Cancer; CEA = carcinoembryonic antigen; idem = the same.

mitomycin C has been extensively studied since the first report by Taylor et al. in 1985 [77] showing a significant reduction in the occurrence of liver metastases and an increase in overall survival. However, only two out of the 12 studies conducted since 1985 were positive [78,79], and unfortunately, the 2 largest and most recent studies have been completely negative. The AXIS study conducted in UK on 3583 patients reported no significant benefit with a maximal absolute gain for the overall 5-year survival of 4% in colon cancer patients [80]. The EORTC study, reported in 1998, conducted on 1235 patients (36%

stage III) with a median follow-up of 5 years, found no difference in favour of IporC using 5-FU alone. The power of this study was sufficient to rule out an absolute difference in overall 5-year survival of 5% [81].

In conclusion, IporC will not give an absolute 5-year survival gain over 5%. In a meta-analysis conducted on the first 10 studies (3499 patients) the absolute 5-year survival gain was 4.7% ($P = 0.006$) [82]. Thus, IporC may not replace systemic chemotherapy, but is perhaps able to ameliorate the results when combined with systemic chemotherapy. The FFCD-9204/EORTC 40911 trial (Table 6) should also be able to answer this question. This combination, however, was not effective in an Italian study, which compared patients treated with adjuvant systemic chemotherapy to a group of patients receiving the same i.v. regimen combined with IporC [83]. However, the power of this study was not able to rule out an absolute 5% survival gain in favour of the combined group (i.v. + IporC).

New biological predictive factors for response, toxicity and survival

Biological factors predictive for tumour chemosensitivity

Several enzymes have been identified in vitro as predictors of response to certain drugs. High thymidylate synthase levels predict for resistance to 5-FU and raltitrexed [84] and p53 status, and the associated apoptotic index, can be predictive of response to biomodulated 5-FU [85]. Although it would be useful in an 'ideal world' to be able to predict those patients who are likely to become resistant to certain therapy options, in reality, it is difficult to obtain biopsy samples and conduct accurate testing [85].

The enzymes topoisomerase I and II [86], dihydropyrimidine dehydrogenase (DPD) [87], UGT1A1 [88] and methylene tetrahydrofolate reductase (MTHFR) [89] have also been identified as possible predictors of response to chemotherapy. However, it is difficult to obtain reliable results from these specific assays and they are unlikely to be employed in the clinic in the short term.

Predictive factors for survival and recurrence rate

The molecular determinants of disease progression in CRC are better defined than for any other malignancy. Stage II (Dukes' B) patients with mutations in codon 12 or 13 of the Ki-*ras* gene are at high risk of developing nodal metastases [90]. p53/Bcl-2 expression predicts survival in patients with CRC [91,92], while circulating p53 antibody also correlates with poor prognosis [93]. Expression of β-catenin, a component of the E-cadherin cell adhesion complex, predicts for the occurrence of liver metastases, distant metastases and for survival [94,95], and vascular endothelial growth factor (VEGF) is predictive of distant recurrence in node-negative patients [96].

However, for the most part, these data have made little impact on predicting the course of the disease, disease spread or survival in the normal clinical setting and, at the present time, it is the presence or absence of a replication error-positive phenotype (RER+) that may begin to change the treatment policy for CRC. It is now generally accepted that there are at least two different kinds of CRC based on their molecular characteristics. One, the most frequent (accounting for approximately 85% of CRCs), has chromosomal mutations in known oncogenes or suppressor genes (*FAP*, K*ras*, *p53* etc.) [92]. The second (accounting for approximately 15% of CRCs) is characterised by chromosomal instability resulting from frequent mismatch repairs of the DNA (MMR) and a RER+ phenotype, usually termed MSI (for microsatellite instability). The former type of CRC (MSS for microsatellite stability) appears to be associated with a worse prognosis and to be less chemosensitive, than the latter type of CRC (MSI), which is predominantly observed in younger patients and in the proximal colon. Important progress has been made recently with the report of biological studies conducted on the tumours of patients who had participated in previous randomised trials, which suggested that patients with MSI seemed to have a better prognosis [97,98] and greater sensitivity to chemotherapy. In one study, an excellent survival after adjuvant 5-FU-LEV (90% at 5-years) compared to the MSI patients who didn't received adjuvant chemotherapy (35% at 5 years) and microsatellite stable (MSS) patients [99].

General conclusions and perspectives

Currently, the therapeutic strategies for the treatment of advanced and metastatic disease have progressed more rapidly than at any time in the last thirty years. In metastatic colon cancer, efficient, palliative chemotherapy regimens increase survival and, in some instances, favour the secondary resection of initially unresectable metastases. There are no differences between the efficacy of the combination of chemotherapy with 5-FU/FA-CPT-11 and 5-FU/FA-oxaliplatin

for time to progression and overal survival [100] and the choice is dependent on the safety data and the availability of the data according to countries. For the treatment of stage III colon cancer in 2001, efficient adjuvant therapy is indicated following surgical resection, but no local chemotherapy or immunotherapy approaches have proved to be either superior or equivalent to 6 months i.v. 5FU-FA chemotherapy. In the very near future, we will know the results of the ongoing adjuvant trials (Table 6) and if the new targeted approaches to treatment are able to improve on the efficacy of the i.v. 5-FU-FA chemotherapy. In stage II colon cancer (Dukes' B, Astler-Coller B2), the benefit of adjuvant treatment is limited and still has not been clearly demonstrated. IperC may exhibit some efficacy, especially in T4 tumours, but clearly new studies are warranted.

The future management of high-risk colon cancer patients will require a multidisciplinary approach in which optimal surgery is combined with systemic chemotherapy, and in some patients with targeted treatments. Better characterisation of the tumour biology will play an important role in the selection of the best drugs and the best routes of administration to be used to improve patient survival and to decrease the risk of toxicity.

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