Adjuvant chemotherapy for stage III colon cancer in 2005: where are we now?

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Introduction

Colon cancer is a very common cancer in economically developed countries, particularly in Europe, North America and Australia, and is one of the leading causes of cancer-related deaths in the Western world. Every year, colorectal cancer is responsible for an estimated 400,000 deaths world-wide.

Seventy percent of patients with colorectal cancer present with apparently localised disease. In these patients, surgery can be curative, but relapses after complete resection are frequent. Colon cancer is not uniformly fatal and there are large differences in survival depending on the stage of the disease. The pathological stage is currently the most important determinant of prognosis. Although the classification system described by Dukes in 1930 is still widely used, it no longer fulfils the requirements of modern tumour staging. It does not take into account distant metastases, the number of lymph nodes involved and carcinomas limited to the submucosa. Therefore, the tumour–node–metastasis (TNM) classification of the American Joint Committee on Cancer (AJCC) is currently recommended for daily routine and in clinical trials. As of 1st January 2003, the newest edition of the *AJCC Cancer Staging Manual, 6th Edition*, is being used to stage colon cancer. This 6th edition stratifies colon cancer stages II and III further by use of T stage (i.e. tumour depth of penetration) and N stage (i.e. number of lymph nodes) (Table 1) [1,2].

Survival rates have been published recently from the Surveillance, Epidemiology, and End Results (SEER) United States (US) national cancer registry from 1st January 1991 through 31st December 2000, based on data from 119,363 patients according to the new AJCC 6th edition staging [3]. Overall 5-year colon cancer-specific survival for this entire cohort was 65.2% [3]. Five-year colon cancer-specific survival by stage was 93.2% for stage I, 84.7% for stage IIA, 72.2% for stage IIB, 83.4% for stage IIIA, 64.1% for stage IIIB, 44.3% for stage IIIC and 8.1% for stage IV cancer. Another large analysis based on the US National Cancer database for an analysis of 50,042 patients from 1987 to 1993 showed a 5-year observed survival rate of 59.8% for stage IIIA, 42.0% for stage IIIB and 27.3% for stage IIIC colon cancer [4].

Table 1
Stages as defined by the American Joint Committee on Cancer (AJCC) in relation to survival[a] [1–4]

Staging system	T stage	N Stage	M stage	5-year survival (%)
I	T1 or T2	N0	M0	93.2[b]
IIA	T3	N0	M0	84.7[b]
IIB	T4	N0	M0	72.2[b]
IIIA	T1 or T2	N1	M0	83.4[b]–59.8[c]
IIIB	T3 or T4	N1	M0	64.1[b]–42.0[c]
IIIC	Any T	N2	M0	44.3[b]–27.3[c]
IV	Any T	Any N	M1	8.1[b]

[a] T1, tumour invades submucosa; T2, tumour invades muscularis propria; T3, tumour invades through the muscularis propria into the subserosa or into non-peritonealized pericolic tissues; T4, tumour directly invades other organs or structures and/or perforates visceral peritoneum; N0, no regional lymph node metastasis; N1, metastasis to 1–3 regional lymph nodes; N2, metastasis to 4 or more regional lymph nodes. M0, no distant metastasis; M1, distant metastasis.
[b] According to SEER database [3].
[c] According to US National Cancer Database [4].

Adjuvant treatment

Since the mid-1990s it has been generally accepted that adjuvant treatment in stage III or lymph-node positive colon cancer decreases relapse rate and improves survival. Several important steps in our knowledge have been made since then.

5-fluororuracil/levamisole for 1 year

The intergroup trial (INT-0035) was the first large-scale study to demonstrate a significant effect of

Table 2
5-fluorouracil-based adjuvant chemotherapy regimens with folinic acid and levamisole[a]

Trial	Regimen	Patients (*n*)	5-year survival rate (%)	
			disease-free	overall
NCCTG-NCIC [12]	5-FU/levamisole (6 months)	230	58	60
	5-FU/FA (Mayo Clinic Regimen) + levamisole (6 months)	225	63	70
	5-FU/levamisole (1 year)	228	63	68
	5-FU/FA (Mayo Clinic Regimen) + levamisole (1 year)	232	57	63
INT 0089 [13]	5-FU/levamisole (1 year)	833	56	63
	5-FU/FA weekly (8 months)	946	59	65
	5-FU/FA (Mayo Clinic Regimen) (6 months)	953	60	66
	5-FU/FA (Mayo Clinic Regimen) + levamisole (6 months)	827	60	67
NSABP C-04 [14]	5-FU/levamisole (1 year)	691	60	70
	5-FU/FA weekly (1 year)	691	65	74
	5-FU/FA weekly + levamisole (1 year)	696	64	73

[a] 5-FU: 5-fluorouracil; FA: folinic acid; NCCTG: North Central Cancer Treatment Group; NCIC: National Cancer Institute of Canada; INT: Intergroup; NSABP: National Surgical Adjuvant Breast and Bowel Project.

postoperative adjuvant treatment in patients with stage III colon cancer. This trial randomised 1296 patients with stage II and III cancer (929 with stage III cancer) to one of three arms: (i) surgery alone; (ii) surgery plus 12 months of levamisole; or (iii) surgery plus 12 months of 5-fluorouracil (5-FU) and levamisole. The study showed a 15% absolute reduction (±40% relative reduction) in the risk of recurrence and a 16% absolute reduction (33% relative reduction) in the overall death rate with a combination of surgery plus 5-FU/levamisole in patients with stage III colon cancer [5,6]. The Dutch Netherlands Adjuvant Colon Cancer Project (NACCP) also demonstrated efficacy of 5-FU/levamisole compared with no adjuvant treatment in a randomised trial of patients with stage II or III colon and rectal cancer [7]. The 5-year survival rate was significantly higher in the adjuvant treatment arm compared with the no adjuvant treatment arm: 68% versus 58%.

5-FU/folinic acid for 6 months

A number of studies in the 1990s have shown the efficacy of 5-FU modulated by folinic acid (FA) when compared with no postoperative treatment. The Canadian and European consortium trial (International Multicentre Pooled Analysis of Colon Cancer Trials; IMPACT) is a combined analysis of three trials that compared adjuvant treatment with high-dose 5-FU and FA with no treatment in nearly 1500 patients: they demonstrated a 22% relative risk reduction in mortality at 3 years in Dukes' C patients [8]. A similar design, but smaller, Italian study showed a 39% reduction in mortality for the patients treated with 5-FU/FA [9]. A North Central Cancer Treatment Group (NCCTG) trial established the efficacy of 6 months' adjuvant therapy with 5-FU/low-dose FA compared with observation after surgery: 74% versus 63% of patients were alive at 5 years [10]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol C-03 indicated a disease-free (73% versus 64%) and overall (84% versus 77%) survival advantage for the 5-FU/FA combination compared with MOF (methyl-CCNU, oncovin, 5-FU) at 3 years for patients with Dukes' stage B and C colon cancer [11]. The control arm in this study (MOF) had previously shown a borderline survival advantage over surgery alone in the adjuvant setting.

Three large adjuvant American trials have been presented more recently, in which several thousands of patients have been treated (Table 2). In a large, randomised study by the NCCTG and the National Cancer Institute of Canada (NCIC), it was shown that there was no additional benefit associated with the administration of a full year of chemotherapy compared with only 6 months of treatment with the same regimen [12]. In the same study, it was shown that, if only 6 months of chemotherapy was administered, patients' survival was significantly inferior with the 5-FU plus levamisole regimen compared with the three-drug combination of 5-FU, levamisole plus FA [12]. INT 0089 trial demonstrated no additional benefit from the addition of levamisole when 5-FU/FA is given and, moreover, 6–8 months

was as efficient as 12 months of 5-FU/levamisole [13]. The NSABP C-04 study demonstrated similar results for 1 year of treatment with 5-FU/levamisole, 5-FU/FA and 5-FU/FA/levamisole [14] (Table 2).

The German Arbeitsgemeinschaft Gastrointestinale Onkologie compared, in the adjCCA-01 trial, 5-FU/FA with 5-FU/levamisole for 12 months in Dukes' C patients. A superior survival in the 5-FU/FA group was shown after a median follow-up time of 82 months: 88.9 versus 78.6 months [15].

Taking into account the increased toxicity of the three-drug combination compared with the combination of 5-FU/FA, an adjuvant treatment with 5-FU/FA for 6–8 months became the generally accepted standard option [16,17].

Regimens of 5-FU: infusional versus bolus regimens

Most of the initial studies in the 1990s were carried out with bolus regimens of 5-FU/FA: the Roswell Park regimen that consists of a weekly administration of FA (500 mg/m^2) plus 5-FU (500 mg/m^2) during 6 weeks followed by 2 weeks of rest for four cycles and the NCCTG/Mayo Clinic regimen that consists of FA (20 mg/m^2) + 5-FU (425 mg/m^2) days 1–5 repeated every 4–5 weeks for 6–7 months. The Quick and Simple and Reliable (Quasar) Collaborative Group in the United Kingdom (UK) has shown, in a very large randomised trial (Quasar-1 study), no difference between a high and low dose of FA in combination with 5-FU and has shown no benefit of adding levamisole to the combination of 5-FU/FA [18].

The French Gercor group studied the role of an infused regimen of 5-FU/FA, the so-called LV5FU2 or de Gramont regimen [19]. This schedule consists of FA 200 mg/m^2 over 2 h, followed by bolus 5-FU 400 mg/m^2, followed by infused 5-FU 600 mg/m^2 over 22 h on days 1 and 2 and repeated every 2 weeks. In a 2×2 factorial design, 905 patients with stage II/III colon cancer were randomised to LV5FU2 or bolus 5-FU/FA (5-FU 400 mg/m^2 and FA 200 mg/m^2 days 1–5, repeated every 28 d). In addition, patients were randomised to a total duration of 24 or 36 weeks of chemotherapy. The study showed no significant differences in disease-free survival (DFS) and overall survival. Rates of grade 3/4 diarrhoea, neutropaenia and mucositis were significantly lower in the LV5FU2 arm compared with a bolus 5-FU/FA regimen [19,20]. Based on this trial and on the superiority and better tolerance of the infusional regimens compared with bolus regimens in patients with metastatic colon cancer, many clinicians consider the LV5FU2 a more optimal option compared with the bolus regimens of 5-FU/FA in the adjuvant treatment of colon cancer.

The Pan-European Trial Adjuvant Colon Cancer (PETACC)–2 trial is investigating this question in more detail in stage III colon cancer. A total of 603 patients have been randomised between a bolus and an infusional 5-FU/FA regimen. Randomisation was finished in early 2004 and results are awaited.

A trial in the UK [21] compared a protracted infusion of 5-FU 300 mg/m^2/d for 12 weeks with a bolus regimen (Mayo Clinic regimen) for 6 months. A total of 801 patients with Dukes' B and C colon and rectal cancer were randomised. There was no difference in relapse-free survival (RFS) and a trend towards an improved 5-year survival in the infusional 5-FU arm: 75.7% versus 71.5% ($P=0.08$) [21]. This trial, however, does not change the concept of the duration of treatment, since rectal and colon cancer patients were both included and since the small sample size precluded final conclusions.

New drugs

Oral fluoropyrimidines

Capecitabine and tegafur+uracil (UFT) are oral fluoropyrimidines that are active in metastatic colorectal cancer. Capecitabine has a superior response rate (RR) compared with bolus 5-FU/FA, while UFT/FA has an identical RR to bolus 5-FU/FA in metastatic colorectal cancer. The time to tumour progression (TTP) and survival of capecitabine and UFT/FA are similar to the TTP and survival of bolus 5-FU/FA in metastatic colorectal cancer. Moreover, the toxicity profile of oral fluoropyrimidines compares favourably with bolus 5-FU/FA.

Several studies have investigated the activity of the oral fluoropyrimidines in the adjuvant treatment of colon cancer. A meta-analysis of three randomised Japanese trials in 5233 patients with stage I, II or III colorectal cancer comparing 12 months of oral adjuvant treatment (oral 5-FU, UFT or carmofur; some patients additionally received mitomycin C) with observation. DFS was improved by the addition of oral fluoropyrimidines with a hazard ratio (HR) of 0.85 ($P=0.001$). Overall survival was also superior in patients receiving oral adjuvant treatment: the HR was 0.89 ($P=0.04$) [22].

The X-Act study randomised 1987 patients with resected stage III colon cancer between capecitabine 2500 mg/m^2/days 1–14 every 21 d and bolus 5-FU/FA (Mayo Clinic regimen: 5-FU 425 mg/m^2 and LV 20 mg/m^2 days 1–5 every 28 d) for 6 months. DFS

Table 3
Oral fluoropyrimidines in the adjuvant treatment of colon cancer

Study		Regimen	Disease-free survival			Relapse-free survival			Survival		
			(%)	HR	*P*	(%)	HR	*P*	(%)	HR	*P*
			3-year			3-year			3-year		
X-Act [23]	Stage III	5-FU/FA	60.6	0.87		61.9	086		77.6	0.84	
	$n=1987$	Capecitabine	64.2	(0.75–1.00)	0.05	65.5	(0.74–0.99)	0.04	81.3	(0.69–1.01)	0.07
			5-year			5-year			5-year		
NSABP	Stage II/III	5-FU/FA	68.3			76.4			78.7		
C-O6 [24]	$n=1608$	UFT/FA	66.9		0.79	74.5		0.52	78.7		0.88

Table 4
Definitions of endpoints in large adjuvant phase 3 trials[a]

	MOSAIC	NSABP C-07	X-ACT	PETACC-3
DFS	• Relapse • New colon cancer • All deaths	• Relapse • New colon cancer • All deaths • New cancers of any type	• Relapse • New colon cancer • All deaths	• Relapse • New colon cancer • All deaths • New cancers of any type
RFS	Not defined	Not defined	• Relapse • New colon cancer • Colon cancer deaths	• Relapse • New colon cancer • All deaths

[a] DFS, disease-free survival; RFS, relapse-free survival.

at 3 years in the capecitabine group was at least equivalent to that in the 5-FU/FA group: $P<0.001$ for the comparison of the upper limit of the HR with the non-inferiority margin of 1.20. Capecitabine improved RFS (HR 0.86, 95%CI: 0.74–0.99, $P=0.04$) and was associated with significantly fewer adverse events than 5-FU/FA (Table 3) [23]. The definitions of disease-free and RFS are detailed in Table 4. The 3-year survival was 81.3% versus 77.6% for capecitabine versus 5-FU/FA (HR 0.84, 95%CI: 0.69–1.01, $P=0.07$).

The NSABP C-06 trial compared adjuvant intravenous 5-FU/FA (Roswell Park regimen: 5-FU 500 mg/m^2 and FA 500 mg/m^2 for 6 of each 8 weeks for three cycles) with UFT/FA (300 mg/m^2/d and FA 90 mg/d days 1–28, each 35 d for 5 cycles) in 1608 patients with stage II or III colon cancer. There was no difference in 5-year DFS (66.9% versus 68.3%) or 5-year overall survival (78.7 versus 78.7%) between the two arms (Table 3). Both regimens had similar toxicity profiles [24].

These studies clearly support the hypothesis that the oral fluoropyrimidines are at least as effective as intravenous 5-FU/FA in the adjuvant treatment of stage III colon cancer. In view of the improved RR in metastatic colorectal cancer, availability of capecitabine, more optimally designed trial in adjuvant treatment and improved tolerance compared with 5-FU/FA, capecitabine is the preferred agent.

Oxaliplatin

The effect of adding oxaliplatin to 5-FU/FA as adjuvant therapy for colon cancer was investigated in two large randomised trials: the MOSAIC and NSABP C-07 trials.

In the MOSAIC trial 2246 patients with stage II and III colon cancer were randomised to 6 months' treatment with LV5FU2 (de Gramont schedule) or FOLFOX4 (identical 5-FU/FA + oxaliplatin 85 mg/m^2 on day 1 of every cycle). Forty percent of patients had stage II colon cancer and 60% stage III. The primary endpoint was the 3-year DFS. The DFS in the MOSAIC trial was defined as the time from randomisation to relapse or death; second colorectal cancers were considered as relapses, whereas non-colorectal tumours were disregarded in the analyses. After a median follow-up of 56.2 months, improved DFS was clear in the FOLFOX4 arm (76.4%) compared with the LV5FU2 arm (69.8%). The HR for DFS was 0.77 (95%CI: 0.65–0.90, $P<0.001$). A statistically significant reduction in the relapse rate was found in the subgroup of stage III colon

Table 5
Combination chemotherapy in adjuvant treatment of colon cancer[a]

Trial	Stage	*n*	Regimen	DFS[b] (%)		HR/*P*-value
				3-year	Long follow-up	
MOSAIC [25,26]	II/III	2246	LV5FU2	72.9	69.8[d]	0.77; $P < 0.001$
			FOLFOX-4	78.2	76.4[d]	
	III[c]	1347	LV5FU2	65.3	61.0[e]	0.76; $P < 0.005$
			FOLFOX-4	72.2	69.7[e]	
NSABP-C-07 [27]	II/III	2492	Bolus 5-FU/FA	71.6		0.79; $P = 0.004$
			FLOX	76.5		
	III[c]	1774	Bolus 5-FU/FA	65.5		0.77/NA
			FLOX	72.2		
CALGB-C89803 [28]	III	1260	Bolus 5-FU/FA	Identical		NA; $P = 0.80$
			IFL			
ACCORD 2 [29]	High-risk III	400	LV5FU2	60		1.19; NS
			IF	51		
PETACC 3 [30]	III	2111	LV5FU2	60.3		0.89; 0.091
			IF	63.3		
	II/III[c]	3005	LV5FU2	66.8		0.88; 0.050
			IF	69.6		

[a] LV5FU2: de Gramont regimen; FOLFOX-4: oxaliplatin + de Gramont regimen; FLOX: oxaliplatin + bolus 5-FU/FA; IFL: irinotecan + bolus 5-FU/FA; IF: irinotecan + de Gramont regimen.
[b] DFS, definitions not identical in different trials: follow-up time different in various trials.
[c] Secondary endpoint.
[d] DFS with median follow-up of 56.2 months.
[e] 4-year DFS.

cancer patients: HR 0.75 (95%CI: 0.62–0.89) with an absolute difference of 8.6%. A trend, but no significant difference in the subgroup of stage II group colon cancer patients was found: HR 0.82 (95%CI: 0.60–1.13) with an absolute difference of 3.5% (Table 5). The survival difference in the total patient population (stage II and III) at 4 years did not yet reach significance: 84.9 versus 82.8% (HR 0.91, 95%CI: 0.75–1.11) [25,26]. In general FOLFOX4 was well tolerated. The all-cause mortality in the trial was 0.5% in both arms. Grade 3/4 neutropaenia occurred in 41.1% in FOLFOX4 versus 4.7% in the LV5FU2 arm. Peripheral neuropathy occurred in 92% of the patients who received oxaliplatin. In total, 12.4% developed grade 3 neuropathy; however this grade 3 persisted at 12 months in only 1.2% and at 24 months in 0.5%. Grade 2 neuropathy was present in 4.2% at 12 months and 2.7% at 24 months and grade 1 neuropathy in 21.8% at 12 months and 13.6% at 24 months, showing an improvement over time in patients who developed peripheral neuropathy [26].

In the NSABP C-07 trial 2492 patients with stage II or III colon cancer were randomised to a bolus regimen of 5-FU/FA (Roswell Park regimen: 500 mg/m^2 FA and 500 mg/m^2 5-FU for 6 of each 8 weeks for 3 cycles) or bolus 5-FU/FA + oxaliplatin (FLOX regimen = identical 5-FU/FA regimen plus oxaliplatin 85 mg/m^2 on day 1, 15 and 29 of each cycle). Twenty nine percent of patients had stage II colon cancer and 71% stage III. The primary endpoint was 3-year DFS, defined as recurrence, second primary colon cancer, new cancers of any type, or death from any cause. The 3-year DFS was improved for patients treated with FLOX compared with 5-FU/FA: 76.5 versus 71.6%. The HR for DFS was 0.79 (95%CI: 0.67–0.93, $P = 0.004$). Survival data are not yet available. In total 85.4% of patients treated with FLOX suffered from neuropathy during treatment and 29.4% at 12 months after stopping treatment. Eight percent of patients had grade 3 neuropathy during treatment and 0.5% at 12 months after stopping treatment. The number of patients with gastrointestinal toxicity was relatively high in both arms. In total, 1.2% died during FLOX treatment and 1.1% during 5-FU/FA [27] (Table 5).

This NSABP trial is very important because it confirms the increased activity of oxaliplatin when

added to 5-FU/FA in the adjuvant treatment of colon cancer. It does not change, however, the concept of the type of 5-FU/FA regimen. In general it is accepted that infusional regimens of 5-FU/FA are a more optimal way of administering 5-FU/FA than bolus regimens. The experience in metastatic colorectal cancer and also in the French Gercor adjuvant of bolus 5-FU/FA versus infused 5-FU/FA supports this choice.

Irinotecan

Three randomised trials have been reported with 5-FU/FA ± irinotecan in the adjuvant treatment of colon cancer: the CALGB 89803, ACCORD 2 and PETACC 3 trials.

The US CALGB 89803 randomised patients with stage III colon cancer to bolus 5-FU/FA (Roswell Park regimen) or bolus 5-FU/FA + irinotecan (IFL = 5-FU 500 mg/m^2, FA 20 mg/m^2 and irinotecan 125 mg/m^2 weekly for 4 weeks on and 2 weeks off for a total of 30 weeks) [28]. The trial closed due to the findings of a higher treatment-related death rate in patients treated with IFL [31]. A total of 1264 patients were enrolled and after a median follow-up of 2.6 years, no difference in DFS or in overall survival was observed [28] (Table 5). Therefore the IFL regimen is not an option in the adjuvant treatment of stage III colon cancer.

The French ACCORD 2 trial compared the LV5FU2 regimen with LV5FU2 + irinotecan 180 mg/m^2 (IF regimen) on day 1 of every cycle for 6 months in high-risk stage III colon cancer. High-risk stage III colon cancer was defined as N2 or N1/N2 with occlusion or perforation. The DFS was not improved with irinotecan: 60% (95%CI: 52.7–66.5) for LV5FU2 and 51% (95%CI: 43.6–57.7). The HR was 1.19 (95%CI: 0.9–1.59) and the toxicity was higher in the IF arm [29] (Table 5).

The PETACC 3 trial is a large trial in which 3005 patients with stage II and III colon cancer were randomised to infused 5-FU/FA ± irinotecan. In total 894 patients had stage II and 2111 stage III colon cancer. The primary endpoint was the 3-year DFS for patients treated with LV5FU2 ± irinotecan in stage III colon cancer patients. The DFS was defined as relapse, death from any cause, second primary colon cancer or second primary cancer other than colon cancer. Secondary endpoints were DFS in pooled population in stage II/III colon cancer, RFS (= DFS with the exclusion of second primary other cancer) in stage III colon cancer, survival and safety (Table 4). There was an imbalance between the two arms: 17% had T4 tumours in the IF and 13% in the LV5FU2 arm ($P = 0.006$). The two arms were not stratified for T stage. Stratification was only for stage II versus III and for centre. At a relatively short follow-up of 38 months the primary endpoint of the trial was not met: the 3-year DFS for stage III colon cancer was 63.3% in the IF arm versus 60.3% in the LV5FU2 arm. The HR for 3-year DFS was 0.89 (95%CI: 0.77–1.11, $P = 0.091$). The DFS for the pooled stage II and III population, a secondary endpoint, was borderline significant: 69.6% versus 66.8%. The HR for stage II/III was 0.88 (95%CI: 0.77–1.00, $P = 0.05$) (Table 5). The RFS for stage III patients was 66% versus 62.2%. The HR for 3 year RFS was 0.86 (95%CI: 0.75–1.00, $P = 0.045$) [30]. Toxicity was slightly higher in the IF arm than in the LV5FU2 arm, but was manageable. The 60-d mortality was <0.5% in both arms, and the mortality within 30 d of the last treatment was <1% in both arms [30].

Monoclonal antibodies

Edrocolomab is a murine IgG2 monoclonal antibody to the glycoprotein antigen 17-1A (or epithelial cell adhesion molecule – EpCAM). An initial very small randomised study in stage III colorectal cancer showed a lower relapse rate for patients treated with edrocolomab compared with observation after surgery alone [32]. A large randomised study in 2761 with stage III colon cancer failed to show an improved outcome for patients treated with 5-FU/FA + edrocolomab compared with 5-FU/FA: the 3-year survival was 74.7% in the edrocolomab/5-FU/FA arm versus 76.1% in the 5-FU/FA alone arm (HR 0.94, 95%CI: 0.71–1.15, $P = 0.53$). Patients treated with edrocolomab had a lower DFS compared with patients with 5-FU/FA: 53% versus 65.5% (HR 0.62, 95%CI: 0.53–0.73, $P < 0.0001$) [33].

Cetuximab is a chimeric monoclonal antibody targeting the epidermal growth factor receptor (EGFR) that is active in irinotecan-refractory EGFR-expressing metastatic colorectal cancer when given alone or in combination with irinotecan. In first-line treatment of metastatic colorectal cancer, non-randomised phase 2 studies showed promising results when cetuximab was combined with FOLFOX or FOLFIRI in EGFR-expressing tumours. Large studies are ongoing or planned in the USA and in Europe in the adjuvant treatment of colon cancer evaluating FOLFOX ± cetuximab.

Bevacizumab is a humanised monoclonal antibody which targets the vascular endothelial growth factor (VEGF), a growth factor essential for tumour

angiogenesis. Randomised studies have shown the increased efficacy when bevacizumab is combined with irinotecan/5-FU/FA and with 5-FU/FA in first-line treatment of metastatic colorectal cancer and with oxaliplatin/5-FU/FA in second-line treatment of metastatic colorectal cancer. Two large studies in the adjuvant treatment of stage II/III colon cancer are ongoing. The NSABP C-08 protocol plans to randomise ~ 2500 patients to 5-FU/FA/oxaliplatin ± bevacizumab. The Avant trial plans to randomise 3450 patients with high-risk stage II and stage III colon cancer between 5-FU/FA/oxaliplatin with 5-FU/FA/oxaliplatin + bevacizumab and the combination capecitabine/oxaliplatin + bevacizumab.

The studies with cetuximab and bevacizumab are designed significantly to improve the 3-year DFS in patients operated for stage II/III colon cancer.

Intraportal or intraperitoneal chemotherapy

Several studies have investigated the role of immediately postoperative administration of intraperitoneal or intraportal chemotherapy. Although a few studies showed a small benefit for patients treated with regional chemotherapy, larger randomised studies could not show an improved outcome for patients treated with systemic 5-FU-based chemotherapy in combination with intraportal or intraperitoneal chemotherapy [34].

Molecular markers

Risk stratification on the basis of histopathological TNM stage has been well documented and is the basis for adjuvant chemotherapy in colon cancer. In addition to the presence or absence of lymph node metastases, the number of histologically examined nodes is generally accepted as a prognostic factor, especially in stage II colon cancer [35]. Tumour grade and histological subtype are also prognostic factors: high-grade (poorly differentiated or undifferentiated) tumours and signet ring cell carcinomas have a worse prognosis than low-grade tumours and than tumours without signet ring cells [3].

In order better to determine the prognosis of patients with colon cancer and to determine groups of patients that are most likely to benefit from adjuvant treatment, better molecular characterisation of the tumours is absolutely necessary. Several molecular markers have already demonstrated clinical efficacy in this setting: loss of heterozygosity (LOH), microsatellite instability (MSI), transforming growth factor beta (TGF-beta) RII mutation and thymidilate synthase (TS) [36]. These molecular markers should be evaluated in prospective randomised studies, so that they can contribute to the determination of an optimal adjuvant strategy in the future. Although several of the large randomised studies discussed in this manuscript evaluated molecular markers (e.g. PETACC 3 trial collected ~1500 tumour blocks for the determination of TS, p53, dihydropyrimidine dehydrogenase (DPD), telomerase, MSI and LOH), many failed to do so.

Endpoints

In most of the trials evaluating new agents, DFS was the primary endpoint. The correlation between 3-year DFS and 5-year survival in adjuvant colon trials has been studied in a large analysis [37,38]. In this analysis of 18 trials including more than 20,000 patients, a strong correlation between 3-year DFS and 5-year survival was shown. A small attenuation in the benefit was observed between these parameters. However, in almost all trials, the presence of a statistically significant DFS advantage at 3 years persisted at 5 years. This analysis, however, did not include oxaliplatin or irinotecan-containing trials. It is therefore currently unknown whether this analysis and correlation is also applicable to newer studies evaluating newer agents.

Another important issue is the lack of uniformity of the definitions of DFS and RFS among the trials, as well as the lack of heterogeneity of the studied patient populations: e.g. stage III alone or stage II and III in the various trials [39]. The definitions of DFS are clearly not identical in all new trials (Table 4). Whether this impacts on the results of the trials is, at this moment, however, unclear. Therefore a plea for uniform definitions of endpoints and definitions of DFS and RFS in the adjuvant treatment of colon cancer is made.

Discussion

Clear progress has been made in adjuvant treatment of colon cancer. It is generally accepted that patients with stage III colon cancer, who are fit to receive adjuvant treatment, should be offered adjuvant chemotherapy. A clinically meaningful reduction in the recurrence rate and improvement in survival has been shown with adjuvant chemotherapy. For many years the standard approach was 6 months of 5-FU/FA. It has been shown more recently that capecitabine is at least as active as intravenous 5-FU/FA in stage III colon cancer and is less toxic than 5-FU/FA and can

therefore replace intravenous 5-FU/FA. Recently it has been demonstrated that the addition of oxaliplatin to 5-FU/FA improves the DFS in colon cancer. Long-term survival results are not yet available. Based on the results of the MOSAIC and NSABP C-07 trials, adjuvant treatment of 6 months of FOLFOX can be recommended in 2005 for patients with stage III colon cancer, who are fit to undergo this chemotherapy.

The PETACC 3 trial needs longer follow-up, before the role of irinotecan can be established in adjuvant treatment of colon cancer.

Many challenges and open questions, however, remain:

- Demonstration of a survival benefit with oxaliplatin/5-FU/FA.
- Understanding of the initial rather disappointing results of irinotecan in adjuvant treatment of colon cancer, although it is active in metastatic colorectal cancer.
- Demonstration of the role of capecitabine in combination regimens in adjuvant treatment of colon cancer.
- Demonstration of the activity of novel targeted agents, such as bevacizumab and cetuximab.
- Design of trials with uniform criteria and definitions of endpoints in adjuvant trials.
- Integration of molecular markers in prognostic classification and in treatment algorithm.
- Better selection of patients who benefit and who do not benefit from adjuvant treatment.
- Evaluation of shorter treatment duration in order to minimise the cumulative toxicity of oxaliplatin.

Conflict of interest statement

None declared.

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