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Combination chemotherapy for metastatic colorectal cancer

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Although CRC is curable by surgery if detected in the early stages, a large proportion of patients will develop metastatic disease. For many years, 5-fluorouracil (5-FU)-based regimens (usually in combination with folinic acid [FA] [leucovorin]) have been the mainstay of chemotherapy for the treatment of advanced CRC (1). (The Advanced Colorectal Cancer Meta-Analysis Project 1992). In recent years, a number of newer agents have shown good activity in CRC. One such drug, the topoisomerase I inhibitor irinotecan, is now considered a standard choice in combination with 5-FU/FA in the first-line treatment of advanced disease (2-4) (Table 1). In addition, 5-FU/FA in combination with the third-generation platinum agent, oxaliplatin, has demonstrated improved response rates and progression-free survival (PFS) compared with 5-FU/FA alone (5-7). Results from a phase III crossover study demonstrated that combinations of 5-FU/FA with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) were similarly effective in terms of response rate, PFS and tolerability, in the first-line treatment of metastatic CRC (8). There is no doubt that treatment regimens introduced in recent years have led to an increase in response rate, and survival now exceeding a median of 20 months in patients with metastatic CRC. However, there is a clear and urgent need for new treatments to improve patient outcome in both the first- and second-line settings.

EGFR and VEGF represent potential targets for novel therapeutic intervention in CRC. The encouraging results from the phase II studies have prompted the initiation of a European two-arm study (the BOND study) (9) which is designed to compare the effects of cetuximab (n=111) with cetuximab plus irinotecan (n=218) in patients with EGFR expressing CRC which have progressed on, or within three months of, irinotecan-based chemotherapy. Patients treated with Cetuximab and Irinotecan had double as high response rate compared to patients receiving Cetuximab alone (23% vs. 11%, p=0.007) and also a significantly longer median time to progression (4.1 vs. 1.5 months, p<0.0001), while the overall survival was not statistically different albeit in favor to the combination treatment (8.6 vs. 6.9 months).
A number of trials have investigated its use in combination with conventional chemotherapy for the first-line treatment of advanced CRC with promising results(10,11).

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Inhibition of the vascular epidermal growth factor (VEGF) by the VEGF antibody bevacizimab has been reported recently. A total of 403 patients were randomized to receive the IFL regimen plus placebo and 412 IFL plus bevacizumab (12). The response rate (35% vs. 45%, p=0.003), time to progression (6.2 vs. 10.4 months, p<0.0001) and overall survival (15.6 vs. 20.3 months, p=0.0003) were all in favor of the combination treatment. This is the first study to demonstrate VEGF inhibition as a successful target.

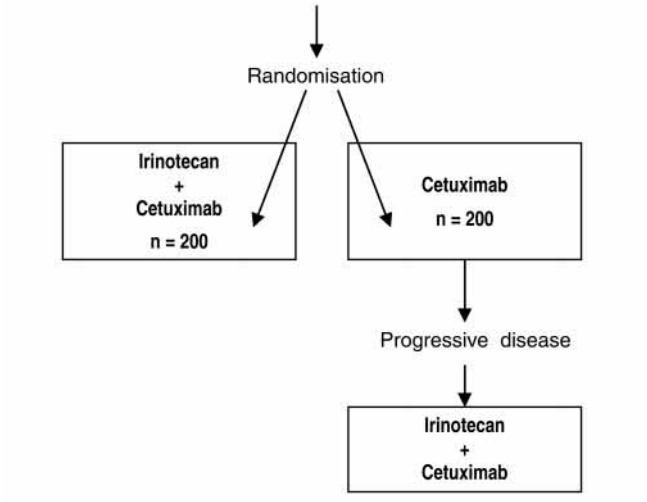

Figure 1. BOND study

Table 1. Recent randomized trials with irinotecan and oxaliplatin in combination with 5-FU/FA in the first-line treatment of metastatic colorectal cancer

		Response		Median survival (months)				
Treatment regimen	No. of patients	Rate (%)	P	PFS	P	Overall	P	Reference
LV5FU2*	420	22%	0.0001	6.2	0.0003	14.7	NS	(5)
+ oxaliplatin		51%		9.0		16.2		
Chronomodulated	200	16%	<0.001	6.1	0.048	19.9	-	(6)
5FU/FA + oxaliplatin		53%		8.7		19.4		
5-FU/FA (Mayo Clinic	238	23%	<0.0001	5.3	<0.0001	16.1	-	(7;13)
regimen)** FUFOX†		48%		7.9		20.4		
5-FU/FA	338	22%	<0.005	4.4	<0.001	14.1	0.031	(2)
+ irinotecan		35%		6.7		17.4		
5-FU/FA	440	21%	<0.001	4.3	0.004	12.6	0.04	(3)
+ irinotecan		39%		7.0		14.8		
AIO	216	32%	<0.001	6.4	<0.001	16.9	0.28	(4)
AIO + irinotecan	214	54%		8.5		20.1		
IFL	264	31%	<0.001	6.9	<0.001	14.8	0.001	(14)
FOLFOX	267	45%		8.7		19.5		
5-FU/FA + irinotecan (FOLFIRI)	226	56%	-	8.5	-	20.4	-	(8)
5-FU/FA + oxaliplatin (FOLFOX)		54%		8.1		21.5		

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