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Colorectal cancer in 2003: state of the art and new developments

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Colorectal cancer (CRC) accounts for 10–12% of all cancers and is second in the league of cancer deaths for men and women in western countries. In Western Europe there were more than 200,000 new cases of CRC and over a 100,000 deaths in the year 2000. Despite increased knowledge about the etiology of the disease and improved treatment strategies nearly 50% of patients still die of their disease. Furthermore, the main cause of death is not recurrence at the primary site, but disease spread, predominantly to the liver. The 5-year survival for patients with metastatic CRC is less than 5%, and while patients with resectable metastases have a 5-year survival of 30%, resectable patients currently represent only 15–20% of patients with liver metastases. The standard therapy for patients with advanced CRC remains palliative 5-fluorouracil (5-FU)-based systemic chemotherapy, which is administered with the aim of improving survival and quality of life (QoL). New combination regimens such as irinotecan/5-FU/folinic acid (FA) and oxaliplatin/5-FU/FA have improved survival [1–5] (Table 1). The recently reported EORTC trial of Köhne *et al.* [5] using irinotecan in combination with the German AIO 5-FU/FA regimen, has produced one of the highest median survival times for first-line chemotherapy in this setting with a median survival time of 20.1 months. The recently published study of the sequential administration of two combination regimens showed that the two regimens FOLFIRI (irinotecan/5-FU/FA [modified de Gramont]) and FOLFOX (oxaliplatin/5-FU/FA [modified de Gramont]) were essentially similar with both achieving high response rates (RRs) and impressive survival when either regimen was administered first-line followed by the other second-line [6]. Patients receiving FOLFIRI followed by FOLFOX achieved a RR of 56% first-line with a median overall survival (OS) of 21.5 months whilst patients receiving FOLFOX followed by FOLFIRI achieved a RR of 54% and a median OS of 20.6 months Table 2 [6]. These

Table 1
Improved survival with new combinations in patients with colorectal cancer

Study	No. pts	5-FU	5-Year overall survival	
			5-FU/FA	+IRI/OXA
Saltz [4]	683	Bolus	12.6	14.8
Douillard [3]	385	de Gramont/ AIO	14.1	17.4
Köhne [5]	430	AIO	16.9	20.1
de Gramont [2]	620	de Gramont	14.7	16.2
Giacchetti [1]	200	Chronomod	19.4	19.9

5-FU, 5-fluorouracil; FA, folinic acid; IRI, irinotecan; OXA, oxalipatin.

Table 2
Relative efficacy and toxicity of FOLFIRI and FOLFOX combinations first-line[6]

	5-FU/FA+	
	Irinotecan	Oxaliplatin
RR	56%	54%
Overall survival (months)	21.5	20.4
G3/4 neutropenia	24%	44%
G3/4 febrile neutropenia	7%	0%
G3 neurological	0%	34%
G3/4 mucositis	10%	1%
G2 alopecia	24%	9%

RR = response rate; 5-FU = 5-fluorouracil; FA = folinic acid.

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differences were not statistically significant, with the two regimens differing only in their toxicity profiles (Table 2). Both studies however clearly indicate that the overall survival rates for patients treated with combination chemotherapy in the palliative setting are gradually creeping upwards and that more patients are well enough to receive second-line therapy. The problem is, 'where do we go next?'

Clearly in the palliative setting, combining irinotecan with oral fluoropyrimidines might be more efficacious and more convenient for the patients whilst new targeted biologicals such as cetuximab [7] and bevacizumab [8], in combination with irinotecan, are showing great promise and should lead to improvements in survival for patients with inoperable metastatic disease. Another objective is to increase the number of patients that are referred for hepatic resections. The emerging evidence that systemic chemotherapy can facilitate the resection of previously unresectable metastases, and the evolution towards a more multidisciplinary approach i.e., surgeons and medical oncologists working together, for the treatment of patients with CRC liver metastases, can only serve to enhance the survival prospects of patients with advanced disease. Furthermore, a more planned approach to the use of systemic chemotherapy in the palliative and adjuvant settings following resection of the primary tumour, and in the case of patients with hepatic metastases in the neoadjuvant, adjuvant and induction settings coupled with surgery, can only serve to increase the chances for longer survival in patients with advanced and metastatic CRC.

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