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Scientific evidence and expert clinical opinion for the management of advanced colorectal cancer by combination chemotherapy

D Alan Anthony and Matthew T Seymour

Introduction

For most of the last three decades, the development of chemotherapy for colorectal cancer has been a process of meticulous optimisation of single-agent therapy with 5-fluorouracil (5FU). Within this straightjacket, considerable progress has been made. Indeed, 5FU has turned out to be a more active and versatile drug than first imagined: it has a well-established evidence base for benefit in both the adjuvant and palliative setting, and when used well it lacks many of the distressing side effects of other cytotoxic drugs.

However, 5FU also has many limitations. For around a third of patients not even temporary stabilisation of disease is obtained, and over the past 10 years it has become clear that even the most active 5FU regimens, when subjected to the rigours of well-conducted, externally reviewed, multicentre, phase III trials, produce WHO objective partial or complete responses in fewer than 30% of patients.

In the early 1980s, Goldie and Coldman (1984) and others (Dexter & Leith 1986) developed models of tumour growth and response to chemotherapy incorporating the concepts of genetic and phenotypic instability, with the emergence of drug-resistant clones during treatment. Goldie and Coldman predicted that the results of chemotherapy would be improved by the use of concurrent or alternating drug schedules, provided that the individual agents were (1) independently active and (2) non-cross resistant. These ideas have underpinned the development of combination chemotherapy for most cancers, but could not be applied or tested in colorectal cancer because only one active agent, 5FU, was available.

At last, this situation is changing. Recent years have seen the arrival of two new drugs, oxaliplatin and irinotecan, each with the properties of independent activity and non-cross resistance, which are prerequisites for combination therapy in the Goldie–Coldman model. In addition, new evidence has emerged for an old drug, mitomycin, suggesting that it, too, may have a role in combination chemotherapy for colorectal cancer.

The rapid burgeoning of knowledge on the cellular and molecular basis of carcinogenesis and metastasis has held the promise of developing drugs targeted to specific components of the pathways involved. A wide range of agents is currently

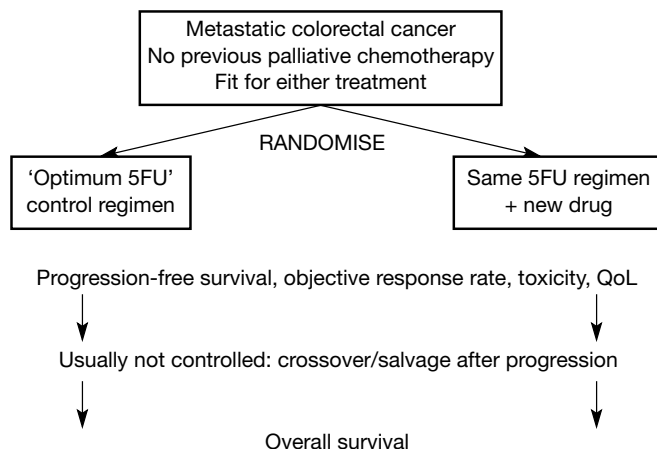


Figure 6.4 General schema for trials of first-line combination chemotherapy.

Table 6.1 Summarised results of first-line 5FU/LV ± irinotecan, oxaliplatin, mitomycin C, phase III randomised trials in advanced colorectal cancer

Reference	Treatment	n	RR (PR + CR) (%)	Median PFS (months)	Median OS (months)
Saltz <i>et al.</i> (2000)	Mayo 5-day 5FU/FA	219	21	4.3	12.6
	vs weekly 5FU/FA/	225	($p = 0.001$)	($p = 0.004$)	($p = 0.04$)
	irinotecan vs weekly irinotecan	223	39 18	7.0 4.2	14.8 12.0
Douillard <i>et al.</i> (2000)	5FU/FA (LV5FU2 or AIO) vs same	187 198	23 ($p < 0.001$)	19 weeks ($p < 0.001$)	14.1 ($p = 0.031$)
	5FU/FA + irinotecan		41	29 weeks	17.4
De Gramont <i>et al.</i> (2000)	5FU/FA (LV5FU2)	210	22	26 weeks	14.7
	vs same 5FU/FA + oxaliplatin	210	($p < 0.0001$) 50	(NS) 36 weeks	($p = 0.0003$) 16.2
Giacchetti <i>et al.</i> (2000)	5FU/FA (chrono)	100	16 ^a	6.1	19.9
	vs same 5FU/FA + oxaliplatin	100	($p < 0.0001$) 53 ^a	($p < 0.05$) 8.7	(NS) 19.4
Ross <i>et al.</i> (1997)	Protracted infusion 5FU vs same 5FU + mitomycin	100 100	38 ($p = 0.024$) 54	23 weeks ($p = 0.033$) 34 weeks	($p = 0.033$)*

CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response; RR, response rate.

*Not significant in the original paper. Updated analysis: Price *et al.* (1999).

^aIncludes confirmed as well as unconfirmed responses.

The design did not quite conform to the scheme in Figure 6.4, because the 5FU/FA schedule in the control arm (the Mayo clinic 5-day monthly schedule) differed from

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