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It is conceivable that sequential use of agents or ‘doublets’ may be as good or superior to multi-drug combinations. Trials to answer these questions are underway.

Oxaliplatin, Irinotecan and Capecitabine

Capecitabine, with its unique advantages and the potential to replace 5FU, is an obvious candidate to test in combination with the newer agents, i.e. irinotecan and oxaliplatin.

The phase I study by Evans et al. (2001) showed encouraging results with capecitabine and oxaliplatin combination. In this study 23 patients with advanced solid tumours who had failed standard chemotherapy were included. Out of nine patients with advanced colorectal cancer five achieved partial responses and three had disease stabilisation. All patients had prior treatment with 5FU-based regimens and four patients had received prior irinotecan. The dose-limiting toxicity was diarrhoea. The results prompted further studies of this combination.

In an ongoing phase II study using capecitabine and oxaliplatin combination as first-line and second-line treatment, early results are promising with the overall response rates of 44% and 22% respectively for first line and second line. Out of the 69 patients entered into the study 43 had no prior chemotherapy whereas 26 patients had one palliative fluoropyrimidine-based therapy. The most common manageable toxicity, as one would expect, is diarrhoea (Borner et al. 2001).

At the recent ECCO meeting, Twelves et al. presented preliminary results of a phase II study of capecitabine and oxaliplatin as first-line treatment for ACRC.

Response rate was over 50%. Grade 3–4 toxicities included vomiting (14%), diarrhoea (8%) and neutropenia (8%). Grade 2 hand–foot syndrome was observed in 24% of patients and only 8% of patients had grade-2 peripheral neuropathy (Twelves et al. 2001).

In a further ongoing phase II study of 35 patients, capecitabine was used in combination with CPT-11 as first-line treatment and preliminary results show overall response rates of 71%. To improve the safety profile of this combination the trial is ongoing with lower doses of irinotecan and final results are awaited.

Some important observations emerge from all of the above completed and ongoing studies of combination therapy. They have higher efficacy (at least in terms of response rate), toxicity is generally acceptable and there is a trend towards survival benefit. Also, capecitabine in the combination therapy makes it ‘patient friendly’ to some extent. If these studies live up to their initial promise it is likely that these combinations will reach clinical practice soon.

What is the best sequence?

With the efficacy of combination chemotherapy proved beyond doubt the next question arises as to what is the best therapeutic sequence. A randomised prospective, multicentre phase III study (GERCOR) addressed this question.

The results were presented at the ASCO 2001 meeting. Patients received either

Table 9.2 Phase III trials in the palliative treatment of metastatic colorectal cancer

<i>Trial name</i>	<i>Academic/ industry</i>	<i>Patients</i>	<i>Line</i>	<i>Control arm</i>	<i>Experimental arm(s)</i>
FOCUS	MRC CR08	2100	First and second	FU/FA Iri on PD	1. FU/FA > FU/FA/Iri 2. FU/FA/Iri 3. FU/FA > FU/FA/oxali 4. FU/FA/oxali
05963	EORTC	554	First	FU/FA/Oxali Chronomod	FU/FA/Oxali flat
N9741	NCCTG	1525	First	FU/FA/Iri	1. FU/FA/Oxali 2. Iri+Oxali
EFC4584	Sanofi	786	First	FU/FA	1. oxali 2. FU/FA/Oxali
EU20034	GERCOR	460	First	FU/FA/Oxali	FU/FA/Oxali (6 high dose) + FU/FA maintenance
CLB9864	CALGB	400	First	FU/FA/Iri	Stratified by racial group
N9841	NCCTG	560	Second	Irinotecan	FU/FA/Oxali
EFC4585	Sanofi	546	Second	Irinotecan	Iri + Oxali
AVF2107g	Genentech	900	First	FU/FA/Iri	Same + RhuMab VEGF
E3200	NCI	693	Second	FU/FA/Oxali	1. FU/FA/Ox + RhuMabVEGF 2. RhuMabVEGF
01-C0093	NCI	168	N/a	FU/FA/Iri+ HAI Fudr + FA	Same + Melphalan isolated Hepatic perfusion
40983	EORTC	330	First	Liver resection	Same + FU/FA/Oxali Pre- and post- operatively
CLB 9481	CALGB	340	First	Liver resection + i.v. FU/FA	Liver resection + HAI Fudr/FA
971151	NCCTG	600	Third	Placebo	Shark cartilage

oxaliplatin arm on all end-points (Goldberg et al. 2002). Finally, a small CALGB trial stratifies patients by racial group and treats all groups with 5FU/FA plus irinotecan with blood sampling to determine the interracial differences in the pharmacokinetics of irinotecan in combination with fluorouracil in terms of SN-38 glucuronidation and toxicity and to determine if there is a significant relationship between UGT1A1 genotype (promoter and/or coding region mutation) and CYP3A4 promoter genotype, toxicity, and pharmacokinetics of irinotecan in this patient population.

The liver metastases studies are evaluating the value of additional systemic or hepatic arterial infusional chemotherapy pre- or post-operatively. A further study about to be launched in Europe (CLOCC) will evaluate the role of radio frequency ablation of liver metastases in addition to chemotherapy for liver only metastatic disease.