The treatment of patients with low tumour burden and/or slow growing disease

Timothy S. Maughan

Gray Institute of Radiation Oncology and Biology, Oxford University, Oxford, United Kingdom

Introduction: assessing prognosis

Predicting prognosis in patients with metastatic colorectal cancer is a difficult art and even for the most experienced oncologist remains a challenge. On radiological grounds, patients with low tumour burden can be identified. The metastatic disease in these patients will have been detected on routine staging or follow up CT scanning either at the time of diagnosis of a primary tumour or on follow up following the previous treatment of a primary tumour. Patients presenting with symptomatic metastatic disease will not fall into this category as the tumour burden will be sufficiently high to have caused symptoms.

At first presentation, it is impossible to predict the pace of the disease purely from radiological analysis, and biochemical and biological factors need to be included in the assessment. Köhne and colleagues [1] analysed the effect on prognosis of various clinical and laboratory parameters in 3825 patients with metastatic colorectal cancer treated with 5-fluorouracil. Following multivariate analysis four factors emerged that enabled the patients to be grouped into three prognostic categories. The factors were ECOG performance status (0, 1 vs 2), level of WBC count (</>10,000/ml), alkaline phosphatase (</>300 IU/l) and number of involved tumour sites (1 vs >1). The high risk group comprised 21% in their validation set and had a median survival of 6.1 months, the moderate risk group (35%) had a median survival of 10.7 months and the low risk group (44%) had a median survival of 15 months. Two other factors which were highly significant in the univariate analysis ($\chi^2 > 100$) but did not survive the multivariate analysis were platelet count (>400,000/l) and albumin (<30 g/l) and should be borne in mind in the clinic. These specific survival times will have changed with the implementation of a wider range of therapies, but the underlying clinical and laboratory parameters remain valid.

In particular the prognostic effect of specific mutations has become important as identification of *KRAS* and *BRAF* mutations is now undertaken routinely in patients with colorectal cancer to identify patients for treatment with EGFR targeted monoclonal antibodies. The prognostic impact of these mutations is not yet finally confirmed. In the RASCAL study [2], 2721 patients with colorectal cancer in all stages were assessed for the effect of *KRAS* mutation on prognosis. Patients in whom a mutation of *KRAS* was detected in the tumour had a higher risk of recurrence ($P < 0.001$) and of death ($P = 0.004$) than those with no mutation in multivariate analysis. This effect was present but marginal in stage 4 patients in this study. In the largest trial in metastatic cancer, the COIN trial [3], the overall survival differed markedly by mutation status irrespective of treatment received. Patients with tumours carrying a *BRAF* mutation had a median overall survival of 8.8 mo, those with a *KRAS* mutation had a median survival of 14.4 mo, with those with *NRAS* mutation very similar median and overlying Kaplan–Meier curves of 13.6 months. In contrast, patients in whom all these three genes were wild-type in the analysed tumour sample had a median survival of 20.1 months. This distinction becomes clearer as the number of mutations assessed increases as patients with the poor prognostic markers of *BRAF* and *NRAS* mutations are otherwise included in the *KRAS* wild-type cohort.

For the purposes of this discussion, patients with low burden or slow growing disease will be firstly those with good performance status (ECOG 0, 1) and a normal WBC count (<10,000/l). These comprise the good prognostic group in Köhne's analysis but also include all those in whom neoadjuvant therapy and resection will be considered. A broader group including more than one metastatic site (for instance lymph node and pulmonary metastases) should also be considered in this discussion. The presence of *BRAF* mutation identifies a group with such poor prognosis that these patients should be considered for clinical trials of targeted approaches. Similarly, though to a less marked effect, patients with *KRAS*

or *NRAS* mutation also need special consideration, though for both of these mutation classes current levels of evidence do not provide any clear guidance on management at this time.

The natural history of the disease with these characteristics

Data on patients in whom treatment is withheld or not given is available from some important studies in the literature. The Nordic group [4] recruited 183 patients between 1985 and 1990, of whom 84% had a Karnofsky score of 100% and 50% had only one site of disease and one third had 2 sites of metastatic disease. Patients were randomised between immediate (Nordic MFL regimen) and deferred chemotherapy ('expectancy'). In the expectancy group, chemotherapy was withheld until symptomatic progression and was given in only 57% of patients after an average of 179 days (range, 5 to 901 days). In this study, median survival in patients treated with 'expectancy' was 9 months compared with 14 months for those treated with primary chemotherapy ($P = 0.02$). Median symptom free survival was 10 months with primary chemotherapy versus 2 months with observation. Only 25 of 92 patients in the expectancy group were symptom free for more than 6 months. However there was no impact on survival beyond 12 to 18 months – so was there a benefit for the patients with slow growing tumours or only for those with more rapidly progressive disease? The authors concluded that 'the choice of a wait and see policy seems to be adequate in this subgroup'.

In contrast, a prospectively planned meta-analysis of two very similar studies conducted in Australia and Canada between 1994 and 1999 [5], each of which had failed to accrue the planned patient numbers, showed no benefit from early chemotherapy. There was no statistically significant difference in overall survival (median 13.0 vs 11.0 months; hazard ratio [HR] 1.15; 95% CI 0.79–1.72; $P = 0.49$) or progression-free survival (10.2 vs 10.8 months; HR 1.08; 95% CI 0.71–1.64; $P = 0.73$). There was no difference in overall quality of life or its individual domains between the two treatment strategies at baseline or at any subsequent time point. The authors concluded that early treatment of asymptomatic patients with metastatic colorectal cancer did not provide a survival benefit or improved quality of life compared to withholding treatment until symptoms occurred.

A Cochrane meta-analysis [6] of patients in trials comparing immediate chemotherapy with deferred chemotherapy or supportive care in metastatic colorectal cancer identified 13 randomised controlled trials including 1365 randomised patients. Individual patient data analyses were performed in a subset of these studies. Death occurred in the supportive care/delayed chemotherapy group in 35% at 6 months, 68% at 12 months, 79% at 18 months and 87% at 24 months. Chemotherapy reduced the risk of death by 35% (95% CI 24–44%). This translates into an improved median overall survival of 3.7 months. However, it is impossible to be clear about the patients included in this analysis and to what extent they had low volume or slowly growing disease.

Taking these data together, the early use of chemotherapy in patients with excellent performance status and low volume disease, without any major adverse prognostic factor remains controversial. Any patients with one of the following factors, should, in my view, be advised to have immediate chemotherapy: cancer related symptoms; WBC >10,000/l; ALP >300 IU/l; Platelets >400,000/l; albumin <30 g/l. The presence of either peritoneal or liver disease would lead me to advise immediate chemotherapy as these disease sites tend to progress more rapidly and lead to intractable symptoms. The presence of *KRAS* mutation certainly confers adverse prognostic implications but does not correlate with non-responsiveness to conventional chemotherapy so patients should commence chemotherapy immediately. Finally for those with *BRAF* mutations, the outlook from current chemotherapies in this group is so poor that such patients should be considered for trials of novel targeted therapy whenever possible.

Is there a role for surgery, local ablation or radiotherapy?

Within the cohort of patients with low volume disease can be found a very important group of patients who may be curable despite the presence of metastatic disease, and oncologists and surgeons are now highly aware of this potential for those with liver metastases. All patients with liver-only metastases should be reviewed in the specialist hepato-biliary multidisciplinary team to assess potential for operability. More controversially, patients with pulmonary metastases may also be suitable for resection. The case is clear cut for patients with a solitary pulmonary nodule which is behaving in a malignant fashion with tumour growth over sequential scans. However beyond that, uncertainty and controversy lies. There are multiple potential therapeutic approaches to such patients with a few (2–10) pulmonary metastases, including resection, ablative and radiotherapeutic approaches. Selection of treatment for patients with 2–10

pulmonary metastases is currently an evidence free zone. In the UK a cardiothoracic surgeon, Tom Treasure, is leading a feasibility study (PulMicc [7]) to assess whether such patients and their oncologists will accept randomisation between chemotherapy only and chemotherapy plus ablative surgery. Addressing this question is challenging as both patients and oncologists have strongly held views at both ends of the spectrum of disease, but it would certainly be of great value if such a trial can be completed.

Another controversial group of patients are those with limited peritoneal metastases. Again data in this area is scarce, however liver surgeons recognise that patients with isolated peritoneal metastases can be surgically cured in the context of combined modality therapy. More frequently, patients with disseminated peritoneal metastases are presented for management discussions at the colorectal multidisciplinary team. Patients with low grade tumours (adenocarcinosis) arising in the appendix and causing pseudomyxoma peritonei are appropriate for peritonectomy and hyperthermic intraperitoneal chemotherapy, the Sugarbaker procedure [8]. This operation and its indications have been the subject of national and international guidelines and consensus statements and the procedure has now been widely accepted as appropriate therapy for carefully staged patients with peritoneal-only metastatic disease of low grade histology. Patients with this condition should be carefully staged and referred to specialist centres for further work up and if appropriate for this major surgical procedure. Median survivals in excess of 20 months have been reported and in those with good features and complete cytoreduction survival of several years is to be expected.

In contrast, those with isolated para-aortic nodal disease have a poor long term outlook and there is no evidence to indicate that a surgical approach is effective in this group of patients; they should be treated with systemic chemotherapy.

First line systemic therapy: Combination versus single agent chemotherapy?

Once the decision has been made to proceed to systemic therapy, the next question that arises is what options should be considered in this patient group with low disease volume in whom it is anticipated that the disease will be slow growing?

International standard regimens routinely combine two chemotherapy agents and often include a biological where health care resources allow. Thus fluorouracil plus either oxaliplatin or irinotecan, with either bevacizumab or cetuximab (for *KRAS* wild-type), are standards of care. However, using three active agents in first line therapy may not be the best or only approach for patients with low volume or slow growing disease.

Five randomised trials have evaluated first line 5-fluorouracil/leucovorin (5FU/LV) monotherapy versus combination therapy with 5FU/LV plus either oxaliplatin or irinotecan. These studies have been reviewed (see ref. [9]) by two of the leading authors in this area. The trials include two MRC trials (FOCUS [10] and FOCUS2 [11]) undertaken in the UK, the Dutch colorectal cancer group trial CAIRO [12], the Fédération Francophone de la Cancérologie Digestive 2000–05 [13] from France and the Sanofi-Aventis LIFE study [14] which recruited in European and other countries (Tables 1, 2). These were strategy trials seeking to define the advantage of an approach to therapy rather than the advantage of a particular agent. The question they have studied is: 'Is it better for patients to receive one drug alone (5FU/LV) followed by other agents in a sequence or to commence with two drugs together?' This series of studies were undertaken in Europe in the period before the advent of biological therapies when there were only three active agents in the treatment of colorectal cancer: fluoropyrimidines, oxaliplatin and irinotecan. The message from these trials was consistent: while combination chemotherapy consistently showed an improved response rate and longer progression-free survival, none of these studies demonstrated a survival advantage of the combination chemotherapy over monotherapies as first line. Three of the trials (FOCUS, CAIRO and LIFE) recruited patients who were fit for full dose combination chemotherapy and of a standard performance status and age as for most trials in first line metastatic disease. All these three showed a very consistent hazard ratio (0.92–0.94) marginally in favour of first line combination therapy, though in none of these trials did this marginal difference reach statistical significance despite the large size of the trials. In the older patients studied in the MRC FOCUS2 trial (median age 75 years) and the FFCD trial (69 yrs), not even this marginal difference was identified, with hazard ratios of 0.99 and 1.05 respectively.

Thus 5FU/FA monotherapy remains an option for the first line treatment of patients with slow growing or small volume metastatic disease. It is still of relevance for the management of patients with low volume and slow growing disease, as it shows that in these patients in whom there is every expectation that patients will be fit enough for second line therapy even if they progress on first line treatment, there is no detriment to overall survival with this approach. Many patients, especially older patients or those

Table 1
Trials comparing 5FU/LV monotherapy versus combination therapy with 5FU/LV plus either oxaliplatin or irinotecan

Trial	No. of patients	Median age (y)	ECOG 2	Sequential arm(s)			Combination arm(s)		Primary endpoint
				1st line	2nd line	3rd line	1st line	2nd line	
FOCUS [10]	2135	64	9%	FU	Ir/IrFU/OxFU	[OxCap/IrCap]	IrFU/OxFU	[OxCap/IrCap]	Survival
CAIRO [12]	803	64	5%	Cap	Ir	OxCap	IrCap	OxCap	Survival
FOCUS2 [11]	460	75	29%	FU/Cap	OxFU/OxCap	[Ir]	OxFU/OxCap	[Ir]	Survival
FFCD [13]	410	69	16%	FU	OxFU	IrFU	OxFU	IrFU	2nd PFS
LIFE [14]	725	62	6%	FU	Ir	–	OxFU	Ir	Survival

Table 2
Trials comparing 5FU/LV monotherapy versus combination therapy with 5FU/LV plus either oxaliplatin or irinotecan

Trial	Results				
	Sequential	Combination	HR	95% CI	p
FOCUS (BvC) [10]	15.1	15.9	0.94	0.83–1.03	NS
CAIRO [12]	16.3	17.4	0.92	0.79–1.08	0.33
FOCUS2 [11]	10.6	11.5	0.99	0.81–1.18	0.91
FFCD [13]	17.0	16.0	1.05	0.84–1.32	0.67
LIFE [14]	15.2	15.9	0.93	0.78–1.10	0.16

with co-morbidities, are very grateful for the gentler palliative chemotherapy schedules that are a feature of fluoropyrimidine monotherapy.

The role of biological therapies?

What relevance do these data have to the management of patients in the current era with biological therapies? Bevacizumab has been demonstrated to improve progression-free and overall survival with limited added toxicity for patients with metastatic colorectal cancer. It is effective in combination with 5FU/FA monotherapy, extending median survival from 14 months to 17.9 months with the addition of bevacizumab [15]. This combination may be successfully used in first line therapy of patients with slow growing or low volume disease. It is of very low toxicity and can provide patients with a year or two of excellent quality of life with their disease well under control and without the added toxicity of combination chemotherapy.

Cetuximab monotherapy has been evaluated in 39 patients with EGFR positive tumours who were chemotherapy naive [16]. One patient had a complete response and three obtained a partial response (10% overall response rate) but median survival was only 12 months. The authors concluded that these data should intensify the search for more precise predictors of response to cetuximab as even in the pre-chemotherapy setting it is only a very small proportion who benefit from EGFR blockade. Interestingly, no data is yet available on the addition of cetuximab to 5FU/FA though a clinical trial is underway. Combination chemotherapy with FOLFIRI plus cetuximab has shown a benefit in patients with *KRAS* wild-type tumours [17], but the use of this triple combination in patients with low volume and slowly growing disease is less relevant than in those with high volume or potentially resectable liver metastases.

Chemotherapy-free intervals

The next question in the management of this patient group is again a strategic question: for how long should chemotherapy be continued and is it feasible to allow periods off chemotherapy without detriment to survival? “Intermittent therapy” given for a limited period, and then re-started either after a predefined interval (predefined treatment) or on progression (repeat therapy), is such an alternative. Concerns remain that intermittent therapy in cancer may result in lessened tumour control or resistance to therapy. However, in breast and prostate cancer, intermittent hormones or cytotoxics have not reduced median overall survival [18–20].

The use of chemotherapy-free intervals in the management of patients with metastatic colorectal cancer

remains controversial. The first study to formally evaluate this was the Medical Research Council (MRC) CR06B trial in which 354 patients with advanced CRC (aCRC) were treated with the de Gramont (5-FU and folinic acid) schedule, continuous infusional 5-FU or raltitrexed [21]. Those with stable or responding disease at 12 weeks were further randomised to continue therapy until progressive disease (PD) or to stop, with the option to restart the same chemotherapy on later PD. There was no evidence of a difference in OS between the two strategies, the hazard ratio of 0.87 even slightly favouring intermittent over continuous treatment (95% CI 0.69–1.09, $P = 0.23$). Patients on intermittent chemotherapy had significantly less toxicity and serious adverse events (SAEs) than those on continuous chemotherapy. This modest RCT gave impetus to the intermittent therapy concept in aCRC and set a precedent for further trials of intermittent combination chemotherapy.

With its cumulative sensory neuropathy, oxaliplatin is an appropriate drug to use in the exploration of intermittent therapy and has been evaluated in three trials, OPTIMOX-1 [22], OPTIMOX-2 [23] and COIN [24]. In OPTIMOX-1, continuous oxaliplatin and 5-FU was compared to a novel strategy of planned oxaliplatin breaks but with continuous 5-FU, whilst in OPTIMOX-2, the OPTIMOX-1 intermittent oxaliplatin strategy was compared to a complete chemotherapy-free interval strategy. Neither of the OPTIMOX trials showed a significant reduction in survival with intermittent therapy. However in the OPTIMOX-2 trial there was a sizeable though statistically non significant difference in overall survival times favouring continuous 5FU. COIN was powered as a non-inferiority trial and failed to show that intermittent chemotherapy, with oxaliplatin and a fluoropyrimidine discontinued after 12 weeks and restarted on progression, was non inferior to continuous chemotherapy.

The GISCAD group [25] has also reported a trial of intermittent chemotherapy using 2 monthly periods of time on irinotecan based chemotherapy alternating with chemotherapy-free intervals. Overall survival was equivalent in the two arms. Further data are awaited on overall survival from the MACRO trial [26] and the NORDIC VII study [27] both of which addressed an intermittent chemotherapy question in the presence of biological therapy in the interval.

On the basis of these data therefore the intermittent treatment strategy with chemotherapy-free intervals should not be used indiscriminately in all patients with metastatic colorectal cancer.

Selection of patients for chemotherapy-free intervals

If this policy cannot be applied indiscriminately, is it applicable to those with slow growing or low volume disease? In the OPTIMOX trials, a further analysis was performed to address this question [22]. The investigators identified 822 patients from the combined database of the two studies who had a 3 month chemotherapy-free interval (CFI) and matched them with similar patients who had not had a three month CFI. In this analysis the authors were not able to identify which patients would benefit from a CFI when examined at baseline before chemotherapy. The data suggested that patients having only 3 months chemotherapy before a CFI had a shorter overall survival.

The same question was addressed in the COIN trial. Planned subset analysis of possible predictive biomarkers revealed that an elevated baseline platelet count was a potentially important predictive factor. One quarter of patients had a raised platelet count at baseline (400,000/ml) and in these patients there was a five month improvement in overall survival comparing continuous therapy with intermittent chemotherapy in this sub-set (test for interaction $P = 0.002$). In comparison, those three quarters of patients with normal platelets at baseline had no loss of overall survival with intermittent chemotherapy (HR 0.96; 95% CI 0.80–1.15) (Fig. 1).

Köhne and colleagues have demonstrated that raised platelet count is a poor prognostic marker though because of its association with raised WBC it was not an independent factor in the multivariate analysis [1]. It is interesting to note that raised platelet count is a poor prognostic factor even in stage 2 disease. A small study [28] showed that 24/148 patients (16%) of patients included in study had platelets >400/mL and that the presence of thrombocytosis correlated with tumour depth and lymphatic invasion. The disease-free and overall survival were significantly reduced in patients with pre-operative thrombocytosis ($P < 0.00001$ in both cases) and the authors postulated that platelets may adversely affect survival via an interaction between tumour and platelets (e.g. secretion of VEGF).

The mechanism may possibly relate to a paracrine feedback phenomenon driven by cytokines including IL6, directly causing thrombocytosis [29]. It may, alternatively, relate to an aspect of immunomodulation driven by T regulatory cells and FOX-P3 epigenetic regulation [30]. If confirmed, the freely available marker of an elevated platelet count at initiation of chemotherapy appears to identify the

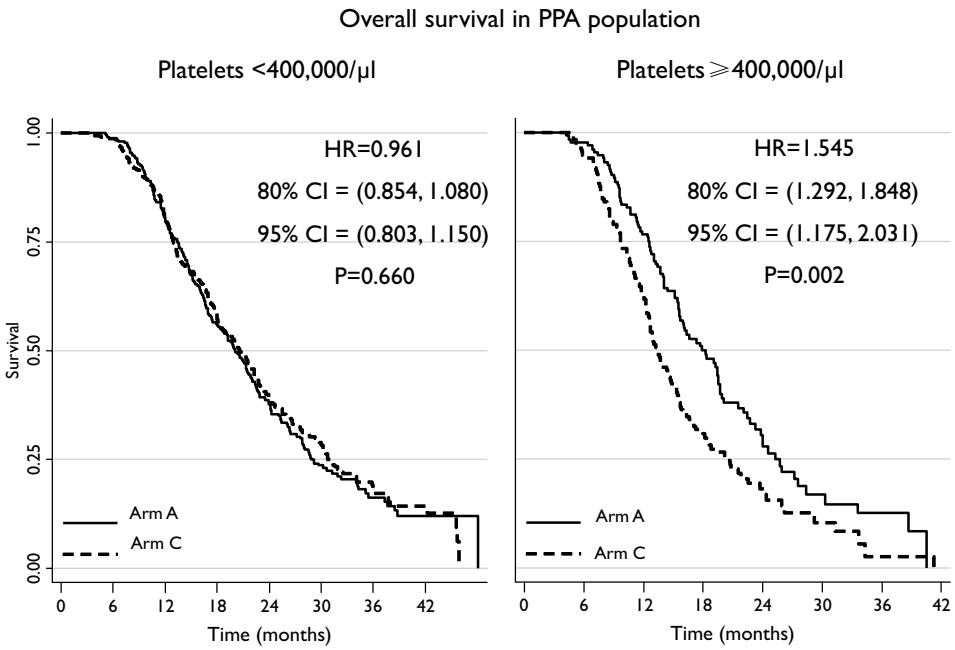

Fig. 1. Kaplan–Meier curves by platelet subgroup at baseline in the COIN trial. Arm A: continuous oxaliplatin based chemotherapy. Arm C: intermittent chemotherapy. In the 28% of patients with platelets ⩾400,000/µl at baseline pre-chemotherapy, a markedly deleterious effect was observed in the patients treated with intermittent chemotherapy (Arm C). Reprinted with permission from the Lancet [3].

patient subset in which continuous therapy is beneficial. In contrast, three quarters of patients with a normal baseline platelet count tolerated periods off treatment with no detriment to OS but benefitted from the reduced time on chemotherapy and less treatment related toxicity. While this observation needs validation in other datasets it raises a very interesting hypothesis about the impact of microenvironmental factors including cytokines on cancer progression. As in rheumatoid arthritis and other inflammatory conditions, chemotherapy can suppress such damaging inflammation for patient benefit and this may be the non specific effect identified here. More specific therapeutic approaches could be considered including cyclo-oxygenase inhibition through non steroidal anti-inflammatories or aspirin, or direct inhibition of interleukin 6 through specific antibody therapy.

Management during the interval

If a decision is taken to allow a patient a chemotherapy-free interval then the patient must be observed closely. This period can be a time of anxiety especially for the carers of the patient. Close observation with regular clinic review and CT scans no less frequently than 12 weekly is a minimum standard. It has been clearly shown by the OPTIMOX group that reintroduction of chemotherapy is important to maintain disease control and prolong survival (see below).

The role of maintenance therapy

There may well be a case for maintenance therapy in the interval between established blocks of chemotherapy. While the OPTIMOX2 trial was underpowered, it certainly suggested an impact of fluoropyrimidine monotherapy as a maintenance strategy [21]. The NORDIC VII [26] study and the MRC COIN-B trial are evaluating the benefit of cetuximab continued as monotherapy during the interval off chemotherapy. The NORDIC VII study compared 3 arms: A: continuous chemotherapy using the Nordic FLOX regimen, B: the same plus cetuximab and C: intermittent FLOX chemotherapy for 12 weeks with continuous cetuximab. Arm C showed no significant improvement in overall survival (C vs A: HR 1.03; 95% CI 0.81–1.32, $P = 0.79$) and the authors concluded that the FLOX given intermittently (stop and go) with continuous cetuximab gives similar survival as treatment until progression. The COIN-B study has completed accrual and outcomes have been submitted to this meeting.

The role of novel therapies as maintenance therapies

The interval in therapy following first line chemotherapy provides a potential opportunity to evaluate the

effect of novel agents as monotherapy at a relatively early point in the process of metastatic disease, before all the further mutations and drug resistance mechanisms have become established in chemo-refractory tumours. The endpoint of progression-free survival from start of maintenance therapy could be compared either with placebo in those countries where it is acceptable to use treatment-free episodes, or versus 5FU or bevacizumab maintenance therapy in other settings. This concept has already been used in the evaluation of immunological treatments and has the potential for more widespread trial design. For instance the DREAM (Double inhibition Reintroduction Erlotinib Avastin Metastatic colorectal cancer) GERCOR (Groupe Coopérateur Multidisciplinaire en Oncologie) study (OPTIMOX3) is evaluating maintenance therapy with targeted drugs alone after chemotherapy with bevacizumab.

Second line therapy

Reuse of first line treatment: One of the key practice points when using any oxaliplatin based intermittent therapy is the importance of reintroduction of oxaliplatin when the disease progresses during a chemotherapy-free interval or on a non-oxaliplatin maintenance approach. In OPTIMOX2 [22] overall response rates after the first FOLFOX reintroduction were 20.4% after 5FU maintenance and 30.3% after a chemotherapy-free interval. Ninety percent of patients who had a partial response at reintroduction previously had a partial response at initial chemotherapy (28 of 31 patients). Control of tumour (partial response plus stable disease) was observed in 59.3% of the patients in arm 1 and 57.6% in arm 2 [22]. Similarly in the COIN trial, in the intermittent therapy arm (Arm C), 325 (40%) started a second 12-week course of chemotherapy after a CFI. Of these, 27% had a partial response, 32% had stable disease and 24% had PD at 12 weeks after re-start. So, significant clinical benefit can be achieved by reusing oxaliplatin especially in those who had previous response. Care must be taken in evaluation of the peripheral neuropathy, and in some patients residual oxaliplatin neuropathy may be dose limiting in this situation. However, in such patients, switching to irinotecan can allow time for the oxaliplatin neuropathy to recover and then oxaliplatin becomes a viable treatment option again at a later stage of the disease.

When to change biological therapy?

One issue that arises in the management of patients with slow growing or low volume disease is that as oncologist we need to make the most of the relatively limited armament of active drugs at our disposal to control the disease in the long term. To that end the issue arises about optimal usage of biological therapies, notably the antibodies against VEGF and EGFR. This area is poor in evidence and no data are as yet available from well designed randomised clinical trials. The AIO 0504/Roche ML18147 Multinational European Trial is recruiting 820 patients and should provide some clearer data in this area. However registry data are available for the use of bevacizumab post progression. In the BRiTE Registry – Patients with Bevacizumab Beyond Progression (BBP) [31] a total of 1953 patients were followed and 1445 patients had data available following first progression. Of these, physicians chose to continue bevacizumab in 642, to discontinue in 531 and to administer no further treatment post progression in 253 patients. With a median follow up of 19.6 months, 932 deaths had occurred. Median overall survival in those with no further treatment after progression was 12.6 months – a poor prognostic group whose disease status was presumably the driving reason why no further therapy was administered. The more interesting data are for the patients in whom the clinicians chose to continue bevacizumab; the median survival was 31 months compared to 19.9 months in those in whom bevacizumab was discontinued. The question arises as to what biases may have influenced the decision of clinicians not to continue bevacizumab. Were there co-morbidities which may have impacted their overall survival? Were these patients less well insured and therefore was there reduced access to further lines of therapy? Only randomised data will settle this issue. However, there is growing consensus that continuation of bevacizumab through second line therapy may be beneficial and this is a practice widely used in the USA.

While this approach is non-contentious in patients with *KRAS* mutant tumours as there is no current biological alternative, in patients with *KRAS* wild-type, the question of when to use an EGFR targeted therapy and when to use a VEGF targeted approach is more interesting. The Crystal trial [17] adding cetuximab to FOLFIRI (5-FU leucovorin and irinotecan) showed a progression-free survival advantage among patients with wild-type *KRAS* tumours with a hazard ratio of 0.68 (95% CI 0.50–0.94), in favour of the cetuximab–FOLFIRI group. On further follow up and with a higher proportion of tumours available for *KRAS* testing, this translated into a survival advantage of 23.5 months versus 20.0 months (HR 0.796; 95% CI 0.67–0.95, $P = 0.0094$) [32]. The greatest benefit of

EGFR targeted monoclonal antibodies has however been seen in the third line setting as discussed below. For the patient group under consideration in this paper, with low volume or slow growing disease, the main reason for selection of an EGFR targeted therapy at this point in time would be if they may become resectable in response to such triple therapy. If that is the case then cetuximab should be used in first line combination. Otherwise, both cetuximab and panitumumab are probably best reserved for third line treatment.

Third line therapy

One of the most fascinating and compelling sets of data in the treatment of colorectal cancer is the benefit from EGFR targeted monoclonal antibodies in chemorefractory patients with *KRAS* wild-type tumours. The randomised trials NCIC CO-17 [33] and Consort [34] tested the effect of single-agent monoclonal antibodies versus best supportive care using respectively cetuximab and panitumumab. The very consistent data from these two trials demonstrate the benefit is limited to those with *KRAS* wild-type tumours in improving the progression-free survival and (in the absence of planned cross over) doubling the survival time from about $4^1/_2$ months to over 9 months. Much more remains to be confirmed about the best selection of patients for EGFR targeted therapy. However, it does appear that it is those patients whose tumours depend on EGFR signaling as indicated by raised EGF ligand mRNA and which do not harbour any mutation of the RAS-RAF pathway. While tumours with high levels of EGFR on immunohistochemistry (IHC) do have a slightly worse prognosis than those with little EGFR expression, EGFR IHC is not predictive of response. Indeed, it appears that it is often patients with a slower disease growth pattern who often respond best to EGFR targeted therapy. This approach therefore is of great relevance to the management of this patient cohort and represents an important step forward in the management of patients with tumours with the relevant molecular characteristics following failure of conventional therapies.

Summary and conclusions

In the evaluation of the wide range of novel therapeutics which have been developed, investigators do not have to be tied to the current paradigm of demonstrating additive efficacy to first line combination therapy. The addition of new agents to FOLFOX regimens has proved a high hurdle at which many promising agents have fallen. In those patients with slow growing disease or low tumour burden both the use of novel agents in a window of opportunity trial before conventional chemotherapy or in combination with single-agent first line chemotherapy may be useful strategies to test efficacy in relatively untreated patients. Further the evaluation of novel therapies in the chemotherapy-free interval allows the use of single-agent treatments early in the disease course with time to progression as a meaningful endpoint for clinical benefit and to give clear data of efficacy.

The most important point from this discussion of the management of patients with slow growing metastatic colorectal cancer is the requirement of the oncologist to have a patient-centred perspective, varying management from standard paradigms to meet patients' needs. We need to consider that this patient may be alive for 3–6 years and we must maximise quality of life as well as survival. That means the patient should be enabled to live as normal a life as possible for as much time as possible. Therefore the selective use of chemotherapy, the use of sequential therapy and of chemotherapy-free intervals is of great importance and can achieve major benefits for our patients.

Conflict of interest statement

The author has no potential conflicts of interest to disclose.

References

1 Köhne CH, Cunningham D, Di Costanzo F, et al. Clinical determinants of survival in patients with 5-fluorouracil based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. *Ann Oncol* 2002;**13**:308–17.

2 Andreyev HJN, Norman AR, Cunningham D, Oates JR, Clarke PA; for the RASCAL Group. Kirsten ras mutations in patients with colorectal cancer: the multicenter "RASCAL" study. *J Natl Cancer Inst* 1998;**90**:675–84.

3 Adams R, Meade AM, Seymour M, et al.; on behalf of the MRC COIN Trial Investigators. Intermittent versus continuous oxaliplatin and fluoropyrimidine combination chemotherapy in the first-line treatment of patients with advanced colorectal cancer: results of the MRC COIN trial. *Lancet Oncol* 2011;**12**:642–53.

4 Nordic Gastrointestinal Tumor Adjuvant Therapy Group. Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomized trial. *J Clin Oncol* 1992;**10**:904–911.

5 Ackland SP, Jones M, Tu D, et al. A meta-analysis of two randomised trials of early chemotherapy in asymptomatic metastatic colorectal cancer. *Br J Cancer* 2005;**93**:1236–43.

6 Best L, Simmonds P, Baughan C. Palliative chemotherapy for advanced or metastatic colorectal cancer (Review). *Cochrane meta-analysis* 2008.

7 Treasure T, Fallowfield L, Lees B. Pulmonary metastasectomy in colorectal cancer: the PulMiCC trial. *J Thorac Oncol* 2010 Jun;**5**(6 suppl):S203–6.

8 Esquivel, J, Sticca R, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a concensus statement. *Ann Surg Oncol* 2007;**14**(1):128–33.

9 Seymour MT, Punt CJA. Sequential chemotherapy for advanced colorectal cancer: Should we ever start with a single cytotoxic agent? *Curr Colorectal Cancer Rep* 2008;**4**(3):130–8.

10 Seymour MT, Maughan TS, Ledermann JA, et al. Different strategies of sequential and combination chemotherapy for patients with poor-prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* 2007;**370**:143–52.

11 Seymour MT, Maughan TS, Wasan HS, et al. Capecitabine (Cap) and oxaliplatin (Ox) in elderly and/or frail patients with metastatic colorectal cancer: The FOCUS2 trial. *Lancet* 2011 May, abstract 9030.

12 Koopman M, Antonini NF, Douma J, et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet* 2007;**370**:135–42.

13 Bouché O, Castaing M, Etienne PL, et al. Randomized strategical trial of chemotherapy in metastatic colorectal cancer (FFCD 2000-05): preliminary results. *J Clin Oncol* 2007;**25** (2007 ASCO Annual Meeting Proceedings Part I), abstract 4069.

14 Pluzanska A, Mainwaring P, Cassidy J, et al. Final results of a randomized phase III study evaluating the addition of oxaliplatin first line to 5-FU followed by irinotecan at progression in advanced colorectal cancer (LIFE study). *J Clin Oncol* 2005;**23** (2005 ASCO Annual Meeting Proceedings Part I), abstract 3517.

15 Kabbinavar FF, Hambleton J, Mass RD, et al. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol* 2005;**23**:3706–12.

16 Pessino A, Artale S, Sciallero S, et al. First line single-agent cetuximab in patients with advanced colorectal cancer. *Ann Oncol* 2008;**19**(4):711–16.

17 Van Cutsem E, Kohne C-H, Hitre E. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;**360**:1408–17.

18 Beex L, Rose C, Mouridsen H, et al. Continuous versus intermittent tamoxifen versus intermittent/alternated tamoxifen and medroxyprogesterone acetate as first line endocrine treatment in advanced breast cancer: an EORTC phase III study (10863). *Eur J Cancer* 2006;**42**:3178–85.

19 Gennari A, Amadori D, De Lena M, et al. Lack of benefit of maintenance paclitaxel in first-line chemotherapy in metastatic breast cancer. *J Clin Oncol* 2006;**24**:3912–8.

20 Rashid MH and Chaudhary UB. Intermittent androgen deprivation therapy for prostate cancer. *Oncologist* 2004;**9**:295–301.

21 Maughan TS, James RD, Kerr DJ, et al. Comparison of intermittent and continuous palliative chemotherapy for advanced colorectal cancer: a multicentre randomised trial. *Lancet* 2003;**361**:457–64.

22 Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer – a GERCOR study. *J Clin Oncol* 2006;**24**:394–400.

23 Chibaudel B, Maindrault-Goebel F, Lledo, et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. *J Clin Oncol* 2009;**27**:5727–33.

24 Adams R, Meade A, Seymour M, et al. Intermittent versus continuous oxaliplatin and fluoropyrimidine combination chemotherapy in the first-line treatment of patients with advanced colorectal cancer: results of the MRC COIN trial. *Lancet Oncol*, in press.

25 Labianca R, Floriani I, Cortesi E, et al. Alternating versus continuous "FOLFIRI" in advanced colorectal cancer (ACC): A randomized "GISCAD" trial. *J Clin Oncol* 2006;**24**(147s): abstr 3505.

26 Tabernero J, Aranda E, Gómez A, et al. Phase III study of first-line XELOX plus bevacizumab (BEV) for 6 cycles followed by XELOX plus BEV or single agent (s/a) BEV as maintenance therapy in patients (pts) with metastatic colorectal cancer (mCRC): the MACRO trial (Spanish Cooperative Group for the Treatment of Digestive Tumors [TTD]). *J Clin Oncol* 2010;**28**(suppl 15s): abstract 3501.

27 Tveit K, Guren T, Glimelius B, et al.; for the Nordic Colorectal Cancer Biomodulation Group. Randomized phase III study of 5-fluorouracil/folinate/oxaliplatin given continuously or intermittently with or without cetuximab, as first-line treatment of metastatic colorectal cancer: The NORDIC VII study (NCT00145314) *Proc ESMO* 2010.

28 Kandemir EG, Mayadagli A, Karagoz B, Bilgi O, Turken O, Yaylaci M, et al. Prognostic significance of thrombocytosis in node-negative colon cancer. *J Int Med Res* 2005;**33**:228–35.

29 Clarke D, Johnson PWM, Banks RE, et al. Effects of interleukin 6 administration on platelets and haemopoietic progenitor cells in peripheral blood. *Cytokine* 1996;**8**:717–23.

30 Lal G, Zhang N, van der Touw W, et al. Epigenetic regulation of Foxp3 expression in regulatory T cells by DNA methylation. *J Immunol* 2009;**182**:259–73.

31 Grothey A, Sugrue MM, Purdie DM, et al. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). *J Clin Oncol* 2008;**26**(33):5326–34.

32 Van Cutsem E, Rougier P, Köhne C, Stroh C, Schlichting M, Bokemeyer C. A meta-analysis of the CRYSTAL and OPUS studies combining cetuximab with chemotherapy (CT) as 1st-line treatment for patients (pts) with metastatic colorectal cancer (mCRC): Results according to KRAS and BRAF mutation status. *EJC Suppl* 2009;**7**(2):345 (abstract 6077).

33 Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008;**359**:1757–65.

34 Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008;**26**:1626–34.