Balancing the efficacy and toxicity of chemotherapy in colorectal cancer

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Abstract: As the therapeutic options for the treatment of colorectal cancer have expanded over the past 20 years, so has the complexity of decision making. The goals of treatment in the palliative, adjuvant and neoadjuvant settings vary and it is not only the efficacy of drugs that influence treatment decisions. Age, performance status, the presence of significant comorbidities and the different treatment regimens and strategies provide medical oncologists with an array of options to attempt to maximize patients' quality of life and longevity.

Keywords: colorectal cancer, combination chemotherapy, fluorouracil, irinotecan, oxaliplatin, performance status, staged chemotherapy, toxicity, treatment breaks

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Introduction

The past 20 years have seen significant advances in the treatment of colorectal cancer (CRC). With more effective drugs, improved surgery, better radiotherapy and a strong randomized clinical trials evidence base, patients now have a higher chance of cure and, when cure is not achievable, longer survival with their disease. However, the natural enthusiasm of oncologists for progress should be tempered by the fact that our treatments remain far from ideal. We treat many patients without benefit, either because their cancer does not respond or because it has already been cured surgically. In the palliative setting, whilst we have seen unequivocal and statistically significant improvements, we still fall far short of achieving what patients want: normal life expectancy. Our advances have done little to lessen the burden of drug toxicity; for although we have learned to reduce the side effects of individual drugs, today's patients are more likely to receive multiple-drug combinations, and for a longer duration.

In this review, we discuss the difficult issues of balancing the positive and negative impacts of cancer drug therapy, and strategies that might affect this balance. We ask oncologists to take a patient-centred approach, and consider the different ways in which patients and their loved ones calculate the tradeoff between benefit and toxicity, and the variable impact that toxicity may have upon quality of life (QoL). Table 1 describes the different treatment options and factors that may be considered in choosing the optimal treatment for a patient.

Treatment of patients with advanced disease

Major improvements in the overall survival (OS) of patients with metastatic disease have been seen over the past two decades. Early randomized data suggest that 5-fluorouracil (5FU) with leucovorin (LV) improves OS by a median of 3.7 months compared with a supportive care strategy [Best *et al.* 2000]. Subsequently, oxaliplatin and irinotecan have each been established to provide a stepwise improvement in response rate and survival outcomes [Goldberg *et al.* 2004; de Gramont *et al.* 2000; Douillard *et al.* 2000]. Most randomized studies performed over the past decade, in which patients received two or all three of these chemotherapy drugs together or in sequence, have produced median OS in the range of 15–20 months, with some studies exceeding 2 years. In contrast, median OS in patients treated with supportive care alone is typically 4–6 months. We must not, however, overestimate the impact of chemotherapy: patient selection, and particularly the exclusion of patients with the worst prognosis from trials involving more intensive chemotherapy regimens, may be an important factor.

Toxicities and selecting optimal treatment regimens

The major toxicities of the cytotoxic drugs used to treat CRC are well described. Much of the clinical research of the 1980s and 1990s focused on establishing an optimal 5FU regimen. Randomized trials and meta-analyses in the 1990s established

Table 1. Treatment aims, options and consideration in colorectal cancer.

	Treatment setting		
	Adjuvant	Neoadjuvant	Palliative
Aim	Reduce risk of cancer recurrence ('cure')	Downstage and potentially allow curative surgery	Maintain/improve quality of life and survival
Treatment options	Single-agent fluoropyrimidine (capecitabine or 5FU)		Single-agent fluoropyrimidine (capecitabine or 5FU)
	Oxaliplatin/fluoropyrimidine	Combination chemotherapy (oxaliplatin or irinotecan plus fluoropyrimidine)	Combination chemotherapy (oxaliplatin/fluoropyrimidine or irinotecan/fluoropyrimidine)
		Three drug combination chemotherapy or doublet plus targeted agent (EGFR mAb)	Chemotherapy plus EGFR- or VEGF-targeted mAbs
Patient factors	Age Performance status Comorbidities Preexisting neuropathy		
Treatment considerations	Recurrence risk	Fitness for combined modality treatment	Staged chemotherapy Treatment breaks

5FU, 5-fluorouracil; EGFR, epidermal growth factor receptor; mAb, monoclonal antibody; VEGF, vascular endothelial growth factor.

that infusional 5FU compared with bolus 5FU regimens (e.g. Mayo clinic regimen) resulted in significantly less severe toxicity, a higher response rate, improved progression-free survival (PFS) and a small difference in OS [Meta-analysis Group in Cancer, 1998a, 1998b; de Gramont *et al.* 1997]. The pattern of severe toxicities experienced when 5FU is delivered in bolus-dosing (e.g. Mayo clinic) or infusion-based (e.g. de Gramont/LV5FU2) regimens varies: bolus dosing resulting in more haematological toxicity (grade 3 or 4 neutropenia in 7.3% Mayo regimen *versus* 1.9% LV5FU2) as well as nonhaematological toxicities such as diarrhoea (7.3% *versus* 1.9%) and mucositis (12.7% *versus* 1.9%) [de Gramont *et al.* 1997]. In contrast, infusional 5FU regimens result in more cases of hand–foot syndrome. The de Gramont regimen, administering a bolus dose of 5FU, followed by a 23 h 5FU infusion delivered on days 1 and 2 every 14 days, and subsequently simplified with the adoption of a 46 h infusion via a central venous line, is widely considered an optimal 5FU regimen. It has also become the preferred partner for combining 5FU with either irinotecan or oxaliplatin because of its improved toxicity profile.

Oral fluoropyrimidines avoid the use of central venous catheters required for infusional 5FU. Capecitabine, an oral fluoropyrimidine carbamate, has been shown to be as effective as and less toxic than bolus 5FU regimens [Van Cutsem *et al.* 2001]. The spectrum of toxicities experienced with capecitabine is consistent with infusional 5FU rather than bolus 5FU regimens. Randomized trials comparing single-agent capecitabine with full-dose modified de Gramont (MdG) have not been performed. The FOCUS2 trial provided a useful comparison of randomized elderly patients or those with a poor performance status (PS) to dose-reduced MdG or capecitabine. In this study similar efficacy and toxicity were observed for capecitabine and MdG but patients receiving capecitabine experienced more grade 3 or 4 toxicity (24% *versus* 36%), although QoL did not differ between the two treatments [Seymour *et al.* 2007b].

Irinotecan has been established as an effective treatment either as a single agent or in combination with 5FU. The characteristic toxicity of single-agent irinotecan is severe diarrhoea, which was experienced by 22% of patients in the pivotal randomized phase 3 study [Cunningham *et al.* 1998]. The IFL regimen (bolus 5FU 500 mg/m^2 and irinotecan 125 mg/m^2 given 4 weeks out of 6) was established as a standard first-line regimen following the publication of a randomized study showing improved response rates and survival compared with the Mayo clinic bolus 5FU regimen [Saltz *et al.* 2000]. However, the overlapping toxicity profiles of bolus 5FU and irinotecan, which both result in high rates of severe diarrhoea, proved problematic [Ledermann *et al.* 2001; Sargent *et al.* 2001]. Subsequent randomized trials in the palliative [Goldberg *et al.* 2004] and adjuvant settings [Saltz *et al.* 2007] showed significantly increased

Table 2. Rates of grade 3 or 4 toxicity associated with standard chemotherapy regimens.

Incidence of grade 3 or 4 toxicity	Regimen				
	LV5FU2 [de Gramont *et al.* 2000]	Capecitabine [Cassidy *et al.* 2002]	FOLFOX-4 [de Gramont *et al.* 2000]	FOLFIRI [Tournigand *et al.* 2004]	Oxaliplatin/fluoropyrimidine plus cetuximab [Adams *et al.* 2009a, 2009b]
Neutropenia	5.3	4	41.7	24	26
Thrombocytopenia	0.5	1.5	2.5	0	–
Infection	1.5	<1	1.5	7	0–5
Nausea	2.0	2	5.7	13	7–14
Vomiting	10.6	2	5.8	10	
Diarrhoea	5.3	13.6	11.9	14	13–25
Neurologic toxicity	0	0	18.2	0	0–10

FOLFIRI, combines irinotecan with an infusional backbone of leucovorin and 5-fluorouracil; FOLFOX-4, oxaliplatin at a dose of 85 mg/m^2; LV5FU2, leucovorin with 5-fluorouracil.

rates of severe toxicity and treatment-related deaths in patients treated with the IFL regimen. The FOLFIRI regimen, combining irinotecan with an LV5FU2 infusional backbone, has demonstrated improved response rates and tolerable rates of severe toxicity, and has subsequently been established as a standard regimen [Tournigand *et al.* 2004; Douillard *et al.* 2000].

Oxaliplatin has limited single-agent activity and is most frequently used in combination with 5FU because of possible synergy between the two drugs. The FOLFOX regimen, combining oxaliplatin with LV5FU2, has been established as a standard oxaliplatin-containing regimen [de Gramont *et al.* 2000]. In addition to the common chemotherapy-related toxicities discussed previously, oxaliplatin characteristically results in transient neurosensory toxicity, often experienced as cold-induced parasthesia, but can result in a dose-dependent chronic peripheral sensory neuropathy [Grothey, 2005]. Table 2 lists the severe grade toxicities experienced with a number of standard chemotherapy regimens.

Treatment strategy: staged or upfront combination

The availability of new active chemotherapy drugs in the late 1990s prompted a number of trials, including the UK MRC FOCUS [Seymour *et al.* 2007a] and Dutch CAIRO [Koopman *et al.* 2007] trials, which compared staged treatment strategies (i.e. starting with fluoropyrimidine monotherapy and upgrading to combination treatment on progression) with initial combination chemotherapy. The CAIRO trial randomized 820 patients to sequential treatment (first-line capecitabine, second-line single-agent irinotecan, third-line capecitabine/oxaliplatin) or combination treatment (first-line capecitabine/irinotecan, second- line capecitabine/oxaliplatin). The median OS was 16.3 months for sequential treatment and 17.4 months for combination treatment ($p = 0.328$).

The FOCUS trial randomized 2135 patients to one of three treatment strategies: staged single-agent chemotherapy (5FU/LV followed by single-agent irinotecan); staged combination chemotherapy (5FU/LV followed by 5FU in combination with either irinotecan or oxaliplatin); or upfront combination chemotherapy with 5FU and irinotecan or oxaliplatin. Survival outcomes across all treatment arms and strategies were very similar. The OS of patients receiving upfront or delayed combination chemotherapy strategies were not statistically different. Patients who received staged single agents had a trend to shorter survival that reached statistical significance for one of the comparisons (*versus* first-line irinotecan/5FU, $p = 0.01$).

The results of the FOCUS and CAIRO trials suggest that for a large proportion of patients presenting with advanced CRC a sequential treatment strategy will result in similar OS, but less initial toxicity, than upfront combination chemotherapy. For instance, grade 3 or 4 lethargy was noted in 13% of patients receiving MdG 5FU in the FOCUS trial compared with 20–21% of patients receiving combination chemotherapy. Similarly, the rates of neutropenia (9% *versus* 19–28%), and nausea and vomiting (4% *versus* 9–10%) were lower among patients receiving MdG. The increased radiological response rate associated with combination chemotherapy

mean that it should be preferred in fit patients considered at risk of bowel obstruction or who may be downstaged and rendered operable.

Duration of therapy

Continuing chemotherapy until intolerance, progression or death is standard practice in many countries. A number of trials over the past 15 years have examined whether it is safe to stop treatment and introduce chemotherapy-free periods without impacting on survival outcomes. Continuing chemotherapy over prolonged periods frequently increases toxicity, particularly fatigue, hand–foot syndrome and oxaliplatin-related neuropathy that can all result in reduced QoL.

The UK MRC CRO6 trial randomized patients whose disease was stable or responding after 3 months of single-agent fluoropyrimidine chemotherapy (de Gramont or Lokich regimen 5FU or raltitrexed) to continue with the same chemotherapy regimen or to enter a treatment break with further chemotherapy reserved for progression [Maughan *et al.* 2003]. Importantly, no clear difference in OS was seen between the two treatment arms (hazard ratio [HR] 0.87 favouring intermittent treatment, 95% confidence interval (CI) 0.69–1.09, $p = 0.23$). Patients receiving intermittent chemotherapy experienced fewer side effects and serious adverse events than patients who continued with chemotherapy.

Intermittent combination chemotherapy strategies have been assessed in a number of clinical trials. OPTIMOX-1 randomized patients to 5FU/oxaliplatin (FOLFOX-4; oxaliplatin dose 85 mg/m^2) until progression or intolerance or FOLFOX-7 using a higher dose of oxaliplatin (130 mg/m^2) for six cycles after which patients whose disease responded continued with maintenance 5FU with oxaliplatin reintroduced after disease progression [Tournigand *et al.* 2006]. No difference in OS was noted between the two treatment arms, indicating that oxaliplatin-free intervals did not shorten OS. A trend to lower rates of severe neuropathy was observed in the intermittent oxaliplatin arm (17.9% *versus* 13.3%, $p = 0.12$), although a greater difference may have been expected had both arms used the FOLFOX-4 regimen.

The OPTIMOX-2 and UK MRC COIN trials subsequently assessed treatment breaks without maintenance 5FU. In OPTIMOX-2 all patients received modified FOLFOX-7 (oxaliplatin dose 100 mg/m^2) with the randomization assessing maintenance 5FU/LV or a complete treatment-free interval [Chibaudel *et al.* 2009]. The trial closed early with only 216 patients randomized. A numerical difference in OS was noted (23.8 *versus* 19.5 months favouring continuous treatment), which although not reaching statistical significance (HR 0.88, $p = 0.42$), raised concerns that treatment-free intervals may be detrimental to patient outcome. The UK MRC COIN trial provides evidence to suggest that any difference in survival is likely to be small and may be offset by differences in toxicity [Adams *et al.* 2009b]. The COIN trial randomized 1630 patients to oxaliplatin/fluoropyrimidine (5FU or capecitabine) until progression or intolerance, or to an intermittent strategy, stopping oxaliplatin/fluoropyrimidine after 12 weeks of treatment. Noninferiority was the primary endpoint for this randomization with a prespecified statistical threshold set as a HR of 1.162 – a value less than this indicating noninferiority. Median OS was 15.6 months for continuous treatment *versus* 14.3 months for the intermittent treatment strategy (HR 1.09). The one-sided upper limit of the 90% CI was 1.17, just exceeding the prespecified threshold and meaning that noninferiority could not be confirmed. However, a difference in median OS of more than 2.3 months could be excluded. Patients receiving intermittent chemotherapy received 10 weeks less chemotherapy and developed significantly less grade 3 or 4 hand–foot syndrome (2% *versus* 4%, $p = 0.044$) and peripheral neuropathy (5% *versus* 19%, $p < 0.001$).

In individualizing care to achieve a patient-centred outcome, the tradeoff between efficacy, toxicity and additional hospital visits associated with different treatment strategies should be discussed. Although continuous treatment may be appropriate in some cases, intermittent treatment strategies may be appropriate and preferred by many patients with metastatic disease, including specific subgroups who may tolerate treatment poorly (e.g. elderly patients and patients with a poor PS).

Influence of performance status and age

Over 85% of patients with CRC are older than 60 years and more than half of patients are over 70 years. Significant proportions of patients also present with a poor PS. However, the majority of patients randomized into clinical trials are under 70 years old, have a good PS (0/1), and limited

comorbidities. Generalizing from selected patients included in randomized studies to unselected patients in clinical practice represents a significant challenge.

In patients with PS0/1, age alone does not appear to be a strong factor influencing outcomes. A retrospective analysis has been performed of 3742 patients, including 614 aged over 70 years, who received 5FU/oxaliplatin chemotherapy in the adjuvant or advanced settings [Goldberg *et al.* 2006]. This demonstrated a modest increase in the rate of significant haematological toxicity, but similar rates of nonhaematological toxicity in patients over 70 years compared with younger patients. Elderly patients also had similar survival outcomes.

A poor PS at presentation does appear to have a profound impact on outcomes even when modern combination chemotherapy is used. A pooled analysis of patients included in randomized trials demonstrated shorter PFS and OS outcomes for patients with PS2 compared with those with PS0/1 (PFS 7.6 months for PS0/1 *versus* 4.9 months for PS2, $p < 0.0001$; OS 17.3 months *versus* 8.5 months respectively, $p < 0.0001$) [Sargent *et al.* 2009]. Analysis of the outcomes of patients with PS2 across five studies randomizing patients to initial 5FU/LV or combination chemotherapy showed a statistically significant improvement in response rates and survival outcomes compared with 5FU/LV, although the absolute differences in OS achieved were modest.

Very few randomized trials have been performed in patients with a poor PS and/or elderly patients. The MRC FOCUS2 trial randomized elderly patients or patients with PS2, judged unfit for full-dose combination chemotherapy, to receive dose-reduced fluoropyrimidine monotherapy, either modified de Gramont 5FU or capecitabine, or the same drugs in combination with oxaliplatin [Seymour *et al.* 2007b]. On comparing 5FU with capecitabine there were no differences in QoL or survival outcomes, but increased rates of severe toxicity were noted in patients receiving capecitabine (24% *versus* 36%). Adding oxaliplatin to either fluoropyrimidine regimen increased the response rate (16–17% *versus* 34–43%) and resulted in a nonsignificant improvement in PFS (HR 0.87, 95% CI 0.71–1.06, $p = 0.16$). The risk of severe toxicity was not significantly increased by the addition of oxaliplatin but there was a lower chance of QoL improvement after 12 weeks of treatment. Consistent with the short survival times observed in the pooled analysis [Sargent *et al.* 2009] OS times in FOCUS2 were short, in the range of 9–12 months across all treatment arms.

The influence patient selection has on outcomes in clinical trials has been highlighted by a prospective series of Scandinavian patients [Sorbye *et al.* 2009]. Patients receiving combination chemotherapy in a clinical trial had a survival of 21.3 months compared with 15.2 months for patients who were not taking part in the trial. The main reason for nonparticipation in a clinical trial was failure to meet the eligibility criteria (69%), with clear differences in prognostic factors observed between the trial and nontrial groups. Patients in the nontrial groups were more likely to be PS2, have peritoneal metastases, have deranged haematology or biochemistry (high white cell count, low haemoglobin and elevated baseline alkaline phosphatase), and have cancer-related pain, significant weight loss and anorexia.

These data highlight the problems of generalizing data from highly selected patient groups to the broader patient population. A small incremental improvement in survival by a median of a few weeks at a cost of significantly increased acute toxicity may be worthwhile in selected patients but may not be tolerated or appropriate for other groups of patients.

Adding targeted agents to combination chemotherapy

Epidermal growth factor receptor (EGFR)-targeted monoclonal antibodies (mAbs) such as cetuximab and panitumumab have both shown activity in CRC. Trials comparing these agents with a supportive care strategy in patients who have already received 5FU, irinotecan and oxaliplatin containing chemotherapies have been performed and a clear relationship between KRAS mutation status and efficacy noted [Amado et al. 2008; Karapetis et al. 2008]. The cetuximab trial noted a significant impact on OS (9.5 versus 4.8 months, HR 0.55, 95% CI 0.41–0.74, $p < 0.001$) among patients with wild-type KRAS with no benefit observed in patients with mutant KRAS (HR 0.98, $p = 0.89$). Toxicity was generally tolerable with an acne-like skin toxicity being characteristic.

Trials combining these agents with chemotherapy, including the MRC COIN trial, have

consistently shown increased rates of overall toxicity compared with chemotherapy alone. COIN included a randomization to continuous oxaliplatin/fluoropyrimidine (5FU or capecitabine) plus or minus cetuximab and significantly increased rates of overall toxicity were observed with the addition of cetuximab. In patients receiving capecitabine and cetuximab, a highly significant increase in the rate of severe diarrhoea was noted, which resulted in the dosage of capecitabine used in the trial being reduced from 1000 mg/m^2 to 850 mg/m^2 twice daily for 14 days [Adams *et al.* 2009a].

Data are still accumulating on the incremental benefit of adding EGFR-targeted mAbs to palliative combination chemotherapy. From the trials conducted so far, it is clear that patients with mutant *KRAS* do not gain a survival benefit and there may be a detriment to receiving EGFR-targeted treatment. The CRYSTAL study randomized patients receiving first-line 5FU/irinotecan (FOLFIRI regimen) with or without cetuximab and demonstrated improved response rates, PFS and OS in patients with wild-type *KRAS* receiving cetuximab [Van Cutsem *et al.* 2009]. However, apart from the randomized phase II OPUS study [Bokemeyer *et al.* 2009], the other trials combining cetuximab or panitumumab with combination chemotherapy have shown, at best, modest activity for the combination. The PRIME [Douillard *et al.* 2009] and COIN [Maughan *et al.* 2009] trials assessed the addition of panitumumab or cetuximab respectively to first-line oxaliplatin/5FU chemotherapy. PRIME showed a small improvement in PFS of 1.6 months in patients with wild-type *KRAS* ($p = 0.02$) receiving panitumumab but no significant difference in OS. The COIN trial showed no significant benefit for the addition of cetuximab in patients with wild-type *KRAS*. Combining EGFR mAbs with standard regimens including bevacizumab has resulted in shorter survival times, increased rates of severe toxicity and worse QoL in patients with wild-type *KRAS* [Hecht *et al.* 2009; Tol *et al.* 2009].

It is likely that other molecular determinants of EGFR-targeted mAb effectiveness will be discovered over the coming years. Currently, however, even among patients with wild-type *KRAS* the additional benefit of adding these agents to combination chemotherapy may be offset by the significant increases in toxicity. The optimal setting for the addition of EGFR mAb treatment (first or second line in combination with chemotherapy or single-agent third-line therapy) is uncertain and may vary according to clinical circumstances.

Whereas adding EGFR-targeted agents to chemotherapy has been associated with a significant increase in the risk of grade 3 or 4 toxicities, the experience with antivascular endothelial growth factor (VEGF)-targeted treatments has been less problematic. Bevacizumab, the leading anti-VEGF targeted treatment, has been assessed in a large, placebo-controlled, randomized study in combination with oxaliplatin/FU (FOLFOX-4) chemotherapy [Saltz *et al.* 2008]. This study demonstrated a small difference in grade 3 or 4 events resulting in treatment discontinuation (30% bevacizumab *versus* 21% placebo) and minor differences in chemotherapy-related toxicities. For instance, gastrointestinal toxicity (32% *versus* 27% for placebo), cardiac disorders (4% *versus* <1%) and hand–foot syndrome (7% *versus* 3%) were all slightly more common in the patients receiving bevacizumab. Adverse events likely to be specifically related to bevacizumab treatment were uncommon, with hypertension the most commonly observed adverse event (4% *versus* 1% for placebo). Bleeding and arterial thromboembolic events were seen in 2% of patients compared with 1% for placebo. The differences in severe toxicities noted with the addition of bevacizumab to chemotherapy therefore appear to be minor with relatively little effect expected on a patient's QoL. For most patients, judgements on the addition of bevacizumab to chemotherapy in the palliative setting can therefore be made based on efficacy data rather than toxicity.

Neoadjuvant chemotherapy

Patients with metastatic disease limited to a single organ, typically the liver, have become a distinct subpopulation of patients with CRC. Surgical resection of metastatic disease leads to long-term survival in approximately 30% of patients, with some data to support the use of perioperative chemotherapy [Nordlinger *et al.* 2008]. Increasingly, patients with metastatic disease initially beyond the scope of curative surgery are being considered for surgical resection following neoadjuvant chemotherapy. Using doublet combination chemotherapy (oxaliplatin/5FU or irinotecan/5FU) has been a standard approach in patients whose disease was not initially resectable, resulting in resection rates of 20–40% in selected series. Using treatment regimens

associated with an increased response rate has been associated with an increased chance of surgical resection [Folprecht *et al.* 2005]. The addition of EGFR mAb therapy to doublet chemotherapy has demonstrated consistent improvements in the response rate in a number of randomized studies. Data from the CRYSTAL trial showed an increased rate of surgical resection among patients receiving cetuximab [Van Cutsem *et al.* 2009]. Using doublet chemotherapy plus cetuximab has therefore been advocated in patients with wild-type *KRAS* based on the CRYSTAL trial data [Nordlinger *et al.* 2009]. Similarly, in patients with *KRAS* mutations, combination chemotherapy with 5FU, oxaliplatin and irinotecan (FOLFOXIRI) has been advocated following the demonstration of response rates of 66% in a randomized study [Falcone *et al.* 2007]. Combining bevacizumab with doublet chemotherapy does not appear to significantly improve response rates [Saltz *et al.* 2008] and is therefore unlikely to significantly improve the chance of surgical resection. Bevacizumab could be used as part of a standard chemotherapy regimen but alternative schedules such as FOLFOXIRI may be considered. Evidence from randomized trials is lacking in this disease setting and clinical trials assessing this subgroup of patients are required. An important consideration in the intensification of treatment in this patient population is the increased toxicity associated with three-drug combination regimens of either doublet chemotherapy plus mAb [Adams *et al.* 2009a; Hecht *et al.* 2009] or triplet combination chemotherapy [Falcone *et al.* 2007; Souglakos *et al.* 2006]. These regimens pose a risk of increased rates of severe toxicity and may not be tolerated by a significant proportion of patients. Careful selection of patients fit enough to undergo intensive chemotherapy and major surgical intervention is therefore vital in this situation.

Adjuvant chemotherapy

Adjuvant 5FU chemotherapy is a standard treatment used in patients with stage 3 (Dukes' C) and high-risk stage 2 (Dukes' B) tumours. Capecitabine and bolus 5FU regimens have proven efficacy and are associated with a low risk of severe toxicity [Twelves *et al.* 2005; Kerr *et al.* 2000]. The addition of oxaliplatin to 5FU improves patient outcomes in the adjuvant setting [Andre *et al.* 2009, 2004, Wolmark *et al.* 2005]. The MOSAIC trial randomized 2246 patients with stage 2 or 3 CRC to receive LV5FU2 or FOLFOX-4 chemotherapy. The OS after 6 years follow up for all patients was 78.5% for FOLFOX-4 *versus* 76% for LV5FU2 (HR 0.80, 95% CI 0.65–0.97, $p=0.023$). Subgroup analysis showed stage-specific 6-year OS rates of 72.9% *versus* 68.7% ($p=0.023$) in patients with stage 3 CRC and 86.9% *versus* 86.8% in patients with stage 2 CRC for FOLFOX-4 and LV5FU2, respectively. The NSABP C-07 trial had a similar design, adding oxaliplatin to adjuvant 5FU chemotherapy, but used a different 5FU schedule and also delivered fewer doses of oxaliplatin than in the MOSAIC trial (nine *versus* 12) [Wolmark *et al.* 2005]. Initial results showed a similar improvement in disease-free survival (DFS) to that observed in the MOSAIC study. Recently presented final results confirm an improvement in DFS, but showed shorter survival times after recurrence in the oxaliplatin arm and an improvement in OS was not seen. A significant interaction between age and some survival endpoints were noted. Patients under 70 years appeared to benefit from the addition of oxaliplatin whereas in patients over 70 years no consistent benefit was seen [Yothers *et al.* 2010]. Analysis of the ACCENT database, including 10,449 patients under 70 years and 2170 patients over 70 years from six randomized studies, demonstrated a significant interaction between age and treatment effect [Jackson McLeary *et al.* 2009]. No differences in outcomes were noted between experimental (combination) chemotherapy and fluoropyrimidine control chemotherapy in patients over 70 years.

Adding oxaliplatin to 5FU increases the incidence of overall grade 3 toxicity and is associated with the occurrence of peripheral sensory neuropathy. Over 90% of patients will experience temporary, classically cold-induced symptoms, with a minority of patients developing persistent symptoms affecting activities of daily living (grade 2 and 3 toxicity). In the MOSAIC trial, grade 3 peripheral sensory neuropathy was noted in 12.5% of patients receiving oxaliplatin during treatment. After 48 months of follow up, the rates of toxicity observed were 11.9% grade 1, 2.8% grade 2 and 0.7% grade 3, respectively [Andre *et al.* 2009]. Similar data have been presented for the NSABP C-07 study [Land *et al.* 2007].

Decisions regarding the use of adjuvant combination chemotherapy are becoming increasingly complex. The approximately 3% incidence of significant long-term peripheral sensory neuropathy

likely to interfere with activities of daily living influences patient decision making relative to the small additional benefit accrued from receiving oxaliplatin. The MOSAIC and NSABP C-07 trials delivered a different total dose of oxaliplatin but both trials noted similar improvements in DFS. Ongoing international trials are assessing shorter periods of oxaliplatin-based chemotherapy in the adjuvant setting (12 *versus* 24 weeks of oxaliplatin/5FU chemotherapy; ISRCTN 59757862) with the aim of assessing noninferiority of shorter periods of treatment as well as examining QoL endpoints.

The relative benefit of chemotherapy is also a key factor in treatment selection for patients in the adjuvant setting. Patients with stage 3 disease are a heterogeneous group and decisions based on age, relative risk of recurrence (N1 *versus* N2 disease), and the additional benefit likely to be achieved by adding oxaliplatin need to be carefully considered. Given the emerging data in patients over 70 years it seems likely that oxaliplatin-based chemotherapy will be used less frequently in this group. Patients with stage 2 disease have an excellent prognosis with or without 5FU-based chemotherapy [Quasar Collaborative Group *et al.* 2007] and patients with high-risk features are selected for treatment. Both C-07 and MOSAIC are underpowered to assess the benefit of adding oxaliplatin to 5FU in patients with stage 2 disease but a trend for improved DFS has been noted. However, any benefit on OS is likely to be very small in absolute terms (<2%) and difficult to justify given the excellent outcomes overall (>80% 5-year OS) and the risk of neurotoxicity.

Conclusions

The optimum treatment strategy for patients with CRC depends on a large number of factors. These include age, PS, the presence of comorbidities and the treatment setting (adjuvant *versus* palliative *versus* neoadjuvant). A high response rate is key in patients with inoperable disease who may be downstaged to allow surgery, but in patients with more widely metastatic disease the key endpoints are OS and QoL. The incorporation of treatment breaks and the use of staged treatment strategies appear to result in little or no detriment to overall survival. Treatment breaks also provide periods of time off chemotherapy that are highly valued by patients as well as resulting in a lower risk of significant toxicity. Targeted therapies are being incorporated into clinical practice and beginning to deliver on some of the promise of personalized medicine. The influence of age, PS and tolerance of treatment should not however be underestimated and will continue to have a major impact on clinical decision making.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

References

Adams, R.A., Meade, A.M., Madi, A., Fisher, D., Kay, E., Kenny, S. *et al.* (2009a) Toxicity associated with combination oxaliplatin plus fluoropyrimidine with or without cetuximab in the MRC COIN trial experience. *Br J Cancer* 100(2): 251–258.

Adams, R., Wilson, R., Seymour, M.T., Meade, A.M., Madi, A., Cassidy, J. *et al.* (2009b) Intermittent versus continuous oxaliplatin-based combination chemotherapy in patients with advanced colorectal cancer: A randomised non-inferiority trial (MRC COIN). *Eur J Cancer* 7(Suppl): 10.

Amado, R.G., Wolf, M., Peeters, M., Van Cutsem, E., Siena, S., Freeman, D.J. *et al.* (2008) Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 26(10): 1626–1634.

Andre, T., Boni, C., Mounedji-Boudiaf, L., Navarro, M., Tabernero, J., Hickish, T. *et al.* (2004) Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 350(23): 2343–2351.

Andre, T., Boni, C., Navarro, M., Tabernero, J., Hickish, T., Topham, C. *et al.* (2009) Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 27(19): 3109–3116.

Best, L., Simmonds, P., Baughan, C., Davis, C., Fentiman, I., George, S. *et al.* (2000) Palliative chemotherapy for advanced or metastatic colorectal cancer. *Cochrane Database Syst Rev* (1): CD001545.

Bokemeyer, C., Bondarenko, I., Makhson, A., Hartmann, J.T., Aparicio, J., de Braud, F. *et al.* (2009) Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 27(5): 663–671.

Cassidy, J., Twelves, C., Van Cutsem, E., Hoff, P., Bajetta, E., Boyer, M. *et al.* (2002) First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. *Ann Oncol* 13(4): 566–575.

Chibaudel, B., Maindrault-Goebel, F., Lledo, G., Mineur, L., Andre, T., Bennamoun, M. *et al.* (2009) Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. *J Clin Oncol* 27(34): 5727–5733.

Cunningham, D., Pyrhonen, S., James, R.D., Punt, C.J., Hickish, T.F., Heikkila, R. *et al.* (1998) Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 352(9138): 1413–1418.

de Gramont, A., Bosset, J.F., Milan, C., Rougier, P., Bouche, O., Etienne, P.L. *et al.* (1997) Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: A French intergroup study. *J Clin Oncol* 15(2): 808–815.

de Gramont, A., Figer, A., Seymour, M., Homerin, M., Hmissi, A., Cassidy, J. *et al.* (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 18(16): 2938–2947.

Douillard, J.Y., Cunningham, D., Roth, A.D., Navarro, M., James, R.D., Karasek, P. *et al.* (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: A multicentre randomised trial. *Lancet* 355(9209): 1041–1047.

Douillard, J., Siena, S., Cassidy, J., Tabernero, J., Burkes, R., Barugel, M.E. *et al.* (2009) Randomized phase 3 study of panitumumab with FOLFOX4 compared to FOLFOX4 alone as 1st-line treatment (tx) for metastatic colorectal cancer (mCRC): The PRIME trial. *European Journal of Cancer* 7S(3): 6, abstract LBA10.

Falcone, A., Ricci, S., Brunetti, I., Pfanner, E., Allegrini, G., Barbara, C. *et al.* (2007) Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: The Gruppo Oncologico Nord Ovest. *J Clin Oncol* 25(13): 1670–1676.

Folprecht, G., Grothey, A., Alberts, S., Raab, H.R. and Kohne, C.H. (2005) Neoadjuvant treatment of unresectable colorectal liver metastases: Correlation between tumour response and resection rates. *Ann Oncol* 16: 1311–1319.

Goldberg, R.M., Sargent, D.J., Morton, R.F., Fuchs, C.S., Ramanathan, R.K., Williamson, S.K. *et al.* (2004) A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 22(1): 23–30.

Goldberg, R.M., Tabah-Fisch, I., Bleiberg, H., de Gramont, A., Tournigand, C., Andre, T. *et al.* (2006) Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. *J Clin Oncol* 24(25): 4085–4091.

Grothey, A. (2005) Clinical management of oxaliplatin-associated neurotoxicity. *Clin Colorectal Cancer* 5(Suppl 1): S38–S46.

Hecht, J.R., Mitchell, E., Chidiac, T., Scroggin, C., Hagenstad, C., Spigel, D. *et al.* (2009) A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol* 27(5): 672–680.

Jackson McLeary, N.J., Meyerhardt, J.A., Green, E., Yothers, G., de Gramont, A., Van Cutsem, E. *et al.* (2009) Impact of older age on the efficacy of newer adjuvant therapies in >12,500 patients (pts) with stage II/III colon cancer: Findings from the ACCENT Database. *J Clin Oncol* 27(15S): abstract 4010.

Karapetis, C.S., Khambata-Ford, S., Jonker, D.J., O'Callaghan, C.J., Tu, D., Tebbutt, N.C. *et al.* (2008) K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 359(17): 1757–1765.

Kerr, D.J., Gray, R., McConkey, C., Barnwell, J. and for the QUASAR Colorectal Cancer Study Group (2000) Adjuvant chemotherapy with 5-fluorouracil, L-folinic acid and levamisole for patients with colorectal cancer: Non-randomised comparison of weekly versus four-weekly schedules – less pain, same gain. *Ann Oncol* 11: 947–955.

Koopman, M., Antonini, N.F., Douma, J., Wals, J., Honkoop, A.H., Erdkamp, F.L. *et al.* (2007) Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): A phase III randomised controlled trial. *Lancet* 370(9582): 135–142.

Land, S.R., Kopec, J.A., Cecchini, R.S., Ganz, P.A., Wieand, H.S., Colangelo, L.H. *et al.* (2007) Neurotoxicity from oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: NSABP C-07. *J Clin Oncol* 25(16): 2205–2211.

Ledermann, J.A., Leonard, P. and Seymour, M. (2001) Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. *N Engl J Med* 345: 145–146.

Maughan, T., Adams, R.A., Smith, C.G., Seymour, M.T., Wilson, R., Meade, A.M. *et al.* (2009) Addition of cetuximab to oxaliplatin-based combination chemotherapy (CT) in patients with KRAS wild-type advanced colorectal cancer (ACRC): A randomised superiority trial (MRC COIN). *Eur J Cancer* 7S(3): 4, abstract LBA6.

Maughan, T.S., James, R.D., Kerr, D.J., Ledermann, J.A., Seymour, M.T., Topham, C. *et al.* (2003) Comparison of intermittent and continuous palliative chemotherapy for advanced colorectal cancer: A multicentre randomised trial. *Lancet* 361(9356): 457–464.

Meta-analysis Group in Cancer (1998a) Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. Meta-analysis Group In Cancer. *J Clin Oncol* 16: 301–308.

Meta-analysis Group in Cancer (1998b) Toxicity of fluorouracil in patients with advanced colorectal

cancer: effect of administration schedule and prognostic factors. Meta-Analysis Group In Cancer. *J Clin Oncol* 16: 3537–3541.

Nordlinger, B., Sorbye, H., Glimelius, B., Poston, G.J., Schlag, P.M., Rougier, P. *et al.* (2008) Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): A randomised controlled trial. *Lancet* 371(9617): 1007–1016.

Nordlinger, B., Van Cutsem, E., Gruenberger, T., Glimelius, B., Poston, G., Rougier, P. *et al.* (2009) Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: Recommendations from an expert panel. *Ann Oncol* 20(6): 985–992.

Quasar Collaborative Group, Gray, R., Barnwell, J., McConkey, C., Hills, R.K., Williams, N.S. *et al.* (2007) Adjuvant chemotherapy versus observation in patients with colorectal cancer: A randomised study. *Lancet* 370(9604): 2020–2029.

Saltz, L.B., Clarke, S., Diaz-Rubio, E., Scheithauer, W., Figer, A., Wong, R. *et al.* (2008) Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. *J Clin Oncol* 26(12): 2013–2019.

Saltz, L.B., Cox, J.V., Blanke, C., Rosen, L.S., Fehrenbacher, L., Moore, M.J. *et al.* (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 343(13): 905–914.

Saltz, L.B., Niedzwiecki, D., Hollis, D., Goldberg, R.M., Hantel, A., Thomas, J.P. *et al.* (2007) Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: Results of CALGB 89803. *J Clin Oncol* 25(23): 3456–3461.

Sargent, D.J., Kohne, C.H., Sanoff, H.K., Bot, B.M., Seymour, M.T., de Gramont, A. *et al.* (2009) Pooled safety and efficacy analysis examining the effect of performance status on outcomes in nine first-line treatment trials using individual data from patients with metastatic colorectal cancer. *J Clin Oncol* 27(12): 1948–1955.

Sargent, D.J., Niedzwiecki, D., O'Connell, M.J. and Schilsky, R.L. (2001) Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. *N Engl J Med* 345: 144–145; author reply 146.

Seymour, M.T., Maughan, T.S., Ledermann, J.A., Topham, C., James, R., Gwyther, S.J. *et al.* (2007a) Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): A randomised controlled trial. *Lancet* 370(9582): 143–152.

Seymour, M.T., Maughan, T.S., Wasan, H.S., Brewster, A.E., Shepherd, S.F., O'Mahoney, M.S. *et al.* (2007b) Capecitabine (Cap) and oxaliplatin (Ox) in elderly and/or frail patients with metastatic colorectal cancer: The FOCUS2 trial. *J Clin Oncol* 25(18S): abstract 9030.

Sorbye, H., Pfeiffer, P., Cavalli-Bjorkman, N., Qvortrup, C., Holsen, M.H., Wentzel-Larsen, T. *et al.* (2009) Clinical trial enrollment, patient characteristics, and survival differences in prospectively registered metastatic colorectal cancer patients. *Cancer* 115(20): 4679–4687.

Souglakos, J., Androulakis, N., Syrigos, K., Polyzos, A., Ziras, N., Athanasiadis, A. *et al.* (2006) FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): A multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). *Br J Cancer* 94(6): 798–805.

Tol, J., Koopman, M., Cats, A., Rodenburg, C.J., Creemers, G.J., Schrama, J.G. *et al.* (2009) Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med* 360(6): 563–572.

Tournigand, C., Andre, T., Achille, E., Lledo, G., Flesh, M., Mery-Mignard, D. *et al.* (2004) FOLFIRI Followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. *J Clin Oncol* 22(2): 229–237.

Tournigand, C., Cervantes, A., Figer, A., Lledo, G., Flesch, M., Buyse, M. *et al.* (2006) 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* 24(3): 394–400.

Twelves, C., Wong, A., Nowacki, M.P., Abt, M., Burris 3rd, H., Carrato, A. *et al.* (2005) Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med* 352(26): 2696–2704.

Van Cutsem, E., Kohne, C.H., Hitre, E., Zaluski, J., Chang Chien, C.R., Makhson, A. *et al.* (2009) Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 360(14): 1408–1417.

Van Cutsem, E., Twelves, C., Cassidy, J., Allman, D., Bajetta, E., Boyer, M. *et al.* (2001) Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: Results of a large phase III study. *J Clin Oncol* 19(21): 4097–4106.

Wolmark, N., Wieand, H.S., Kuebler, J.P., Colangelo, L. and Smith, R.E. (2005) A phase 3 trial comparing FULV to FU/LV + oxaliplatin in stage 2 or 3 carcinoma of the colon: Results of NSABP Protocol C-07. *J Clin Oncol* 23(Suppl): abstract 3500.

Yothers, G.A., O'Connell, M.J., Colangelo, L., Kuebler, J.P., Lopa, S., Findlay, M.P. *et al.* (2010) 5-FU and leucovorin (Lv) with or without oxaliplatin (Ox) for adjuvant treatment of stage II and III colon cancer: Long-term follow-up of NSABP C-07 with survival analysis. In: *Proceedings of the ASCO Gastrointestinal Cancers Symposium*, Orlando, Florida, abstract 401.