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New approaches for the treatment of colorectal cancer in the adjuvant setting

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Abstract

The value of adjuvant chemotherapy for some patients with stage III colorectal cancer has been established but the situation is less clear for stage II disease. Currently, infusional or bolus 5-fluorouracil (5-FU)/folinic acid (FA) is the treatment of choice but its success is limited and the use of combination therapies is now being investigated. The efficacy of irinotecan in metastatic disease has prompted its use in the adjuvant setting. A number of phase II and randomised phase III trials are investigating the role of irinotecan in combination with capecitabine in the metastatic setting. The role of irinotecan in combination with infusional and/or bolus 5-FU/FA and capecitabine is also under extensive review in the adjuvant setting. Adjuvant therapy with the combination of oxaliplatin/5-FU/FA has been shown to prolong three-year disease-free survival. The overall survival data for this study are not yet available. The use of targeted agents, which are not associated with the toxicities commonly associated with cytotoxic chemotherapy, are being investigated and because of their good safety profile have particular application for this stage of the disease. Biological markers which can help to identify those patients whose disease has a high likelihood of recurrence or those most likely to respond to chemotherapy will help to direct the optimum use of adjuvant therapy.

Keywords: Adjuvant; Colorectal; Irinotecan; Markers; Oxaliplatin; Stage III

1. Introduction

Theoretically, localised colorectal cancer is potentially curable by surgery alone, provided that the resection margins are clear. The presence of covert micrometastases, however, will eventually lead to recurrence of the disease. In patients with stage I and II disease, the likelihood of micrometastases is relatively small. Stage III patients, however, are more likely to harbour micrometastases, and, therefore to suffer relapse. The aim of adjuvant chemotherapy is to ideally eradicate microscopic disease and so reduce the risk of disease recurrence.

2. FU/FA-based chemotherapy

The efficacy of adjuvant chemotherapy to improve the outcome of patients with stage III (Dukes stage C) colon cancer was reported in a phase III trial by Moertel and colleagues in 1995 [1], and is generally well accepted [2]. Over 900 patients were randomised to receive bolus 5-fluorouracil (5-FU) plus levamisole or levamisole alone, or to observation only. The combination of 5-FU and levamisole significantly reduced both the recurrence rate and death rate. This was confirmed by a pooled analysis of data from seven phase III randomised trials, involving over 3300 patients with stage II and III disease who received either 5-FU/folinic acid (FA) or 5-FU/levamisole following surgery or no further treatment [3]. According to this analysis, adjuvant treatment again significantly increased the time to tumour recurrence and prolonged overall survival. Importantly, the efficacy

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and toxicity of adjuvant therapy did not appear to be influenced by age, confirming that patients of all ages can benefit from this approach.

Initially, 5-FU combined with either FA or levamisole was used as adjuvant treatment. However, randomised trials showed that 5-FU/FA was significantly better than 5-FU/levamisole in reducing tumour recurrence and improving survival [4]. Adding levamisole to the 5-FU/FA combination did not further improve patient outcome [5,6]. It was also reported that six months of chemotherapy was as effective as 12 months of chemotherapy in terms of survival [7]. The QUASAR collaborative group investigated the benefits of increasing the dose of FA in combination with bolus 5-FU [6]. In a trial of nearly 5000 patients, high-dose FA (175 mg) appeared to produce no survival benefit over low-dose FA (25 mg). In a subset analysis of 746 patients from the QUASAR trial, adjuvant chemotherapy was shown to have only a minor impact on patient quality of life; this was related to the expected toxicity associated with the chemotherapy regimens and the degree of toxicity [8]. In the late 1990s, trials in metastatic colorectal cancer showed that administering 5-FU by infusion rather than by bolus injection did not improve survival, but led to an improved response rate and median progression-free survival, and better tolerability [9,10]. Recently reported results from two randomised trials confirmed the better tolerability of infusional 5-FU+/−FA [11,12]. Twelve weeks of infusional 5-FU (300 mg/m^2) was as effective as six months of bolus 5-FU (425 mg/m^2)/FA. Grade 3/4 toxicity was significantly lower and quality of life scores higher with infusional compared with bolus 5-FU. The French study has compared the infusional 5-FU/FA regimen (semi-monthly for 2 consecutive days) as dl or l-FA (200 or 100 mg/m^2, respectively) as a 2-h infusion followed by a 400 mg/m^2 5-FU bolus and 600 mg/m^2 5-FU as a 22-h continuous infusion, with a bolus 5-FU/FA regimen monthly for 5 consecutive days as a 15 min infusion of FA followed by 400 mg/m^2 5-FU as a 15 min infusion in stage II and III colon cancer. It was shown that the infusional and bolus regimens were equally effective, but that the bolus regimen lead to more adverse events [12]. Patient numbers however were relatively low in both studies. The ongoing phase III PETACC-2 trial is evaluating the benefits of adjuvant high-dose infusional 5-FU/FA compared with standard bolus 5-FU/FA in stage III colon cancer. When these results are available, we will have a clearer idea of the relative roles of bolus and infusional 5-FU for adjuvant therapy.

Despite the progress made in adjuvant chemotherapy, patients with resected disease will generally suffer recurrence and eventually die from their disease, underlining the need for better, more effective management approaches. Irinotecan and oxaliplatin are currently two of the most active agents in the management of metastatic colorectal cancer [13–15]. Based on their efficacy in advanced disease, they have been investigated in the adjuvant setting.

3. Irinotecan plus fluoropyrimidines

3.1. Irinotecan plus 5-FU/FA

Irinotecan is currently under investigation in a number of studies in the adjuvant setting (Table 1). The ACCORD 2 trial is comparing 12 cycles of bolus and infusional 5-FU (400 mg/m^2 bolus and 600 mg/m^2 22-h continuous infusion)/FA alone or in combination with irinotecan (180 mg/m^2, day 1, every 14 days) [16]. Four hundred patients with stage III disease and a high risk of recurrence were randomised to treatment. As of May 2003, interim safety results on 280 of these patients were available. The relative dose intensities (RDI) for 5-FU were 0.98 for the 5-FU/FA arm and 0.94 for the irinotecan/5-FU/FA arm. The RDI for irinotecan was 0.90. The incidence of grade 3/4 neutropenia and febrile neutropenia was higher in the irinotecan arm (28% and 3%) compared with the 5-FU/FA arm (4% and 0%). In addition, grade 3/4 diarrhoea, alopecia and vomiting were higher in the irinotecan arm. There were nine serious adverse events in the 5-FU/FA arm and eight in the 5-FU/FA/irinotecan arm. It is interesting to note that the incidence of grade 3/4 febrile neutropenia and diarrhoea with 5-FU/FA/irinotecan was similar to that reported for this combination used as first-line therapy for the treatment of metastatic colorectal cancer [13] (Table 2). However, the frequency of grade 3/4 neutropenia was substantially lower in the adjuvant trial (28% versus 46%). The primary endpoint of the ACCORD 2 trial is three-year event-free survival, and the efficacy results are eagerly awaited.

The potential of the combination of irinotecan/5-FU/FA as adjuvant therapy is actually being investigated in the large phase III PETACC-3 trial. This open-label randomised trial is comparing high-dose infusional 5-FU/FA alone with the same regimen in combination with irinotecan in patients with stage III colorectal cancer who have undergone curative resection. In the irinotecan arm, patients are randomised to receive 5-FU/FA according to either the modified AIO regimen plus irinotecan (80 mg/m^2 weekly), or the De Gramont regimen plus irinotecan (180 mg/m^2, days 1, 15, 29) (Table 1). The primary endpoint of this trial is disease-free survival. Recruitment was completed in 2002 and 2333 stage III patients have been entered into the trial. The first efficacy results are expected in 2004 and should clarify the role of irinotecan/5-FU/FA as adjuvant therapy. This trial also attempts to clarify the prognostic value of several important molecular markers in colon cancer.

Table 1
Ongoing randomised trials of irinotecan-based adjuvant chemotherapy for patients with stage III and II colorectal cancer

Trial	Disease stage	Treatment regimens	Patients	Endpoints
ACCORD 2	III (high risk)	Arm A: FA (200 mg/m^2) plus bolus and infusional 5-FU (400 mg/m^2 bolus and 600 mg/m^2 22-h CI) alone (days 1–2, every 14 days) (LV5FU2) Arm B: LV5FU2 in combination with irinotecan (180 mg/m^2, day 1, every 14 days). For 12 cycles	400	Three-year disease-free survival, safety, overall survival
PETACC-3	III	Arm A: Weekly AIO regimen (FA [500 mg/m^2] plus high-dose infusional 5-FU [2000 mg/m^2 24-h CI]) or two-weekly LV5FU2 regimen Arm B: Weekly AIO regimen (FA [500 mg/m^2] plus high-dose infusional 5-FU [2000 mg/m^2 24-h CI]) plus irinotecan 80 mg/m^2 or two-weekly LV5FU2 (FA [200 mg/m^2] plus bolus and infusional 5-FU [400 mg/m^2 bolus and 600 mg/m^2 22-h CI] alone [days 1–2, every 14 days]) plus irinotecan (180 mg/m^2)	2333	Three-year disease-free survival, safety, overall survival, translational research
QUASAR II	III	Arm A: Bolus 5-FU/FA (370/20 mg/m^2) weekly for 30 weeks OR days 1–5, every 4 weeks for 24 weeks OR modified de Gramont regimen (FA 200 mg/m^2, bolus 5-FU 400 mg/m^2 followed by 2.8 g/m^2 46-h CI) every 2 weeks for 12 cycles Arm B: Irinotecan (250 mg/m^2, day 1) plus capecitabine (1 g/m^2 twice daily, days 1–14) every 3 weeks for 8 cycles Arm C: Treatment as in Arm B plus bevacizumab (7.5 mg/kg, day 1, every 3 weeks for 16 cycles)	3450	Three-year disease-free survival, safety, overall survival, translational research
CALGB C89803	II and III	Roswell Park schedule (FA 500 mg/m^2 over 2 h plus 5-FU 500 mg/m^2 given 6 weeks on, 2 weeks off $\times$ 4 cycles) or the IFL schedule (irinotecan 125 mg/m^2 followed by FA 20 mg/m^2 and 5-FU 500 mg/m^2 given 4 weeks on and 2 weeks off)	1263	Three-year disease-free survival, safety, overall survival, translational research
AERO	II and III rectal cancer	Intermittent bolus and infusional 5-FU (LV5FU2) plus irinotecan, compared with LV5FU2 alone in stage II and III rectal cancer.	600	Five-year disease-free survival, safety, overall survival
PETACC-4	II	FOLFIRI regimen (FA 400 mg/m^2 followed by 5-FU 400 mg/m^2 as an IV bolus and then 5-FU 2400 mg/m^2 as a 46 h continuous infusion in combination with irinotecan 180 mg/m^2 on day 1, administered every 2 weeks) or the AIO regimen plus irinotecan (FA 500 mg/m^2 + 5-FU/24 h 2000 mg/m^2 plus irinotecan 80 mg/m^2 $\times$ 6 weeks) or the TTD regimen plus irinotecan (irinotecan 80 mg/m^{2}plus 5-FU/48 h infusion 2250 mg/m^2 weekly $\times$ 6 weeks)	1976	Five-year disease-free survival, safety, overall survival, translational research

FA, folinic acid; 5-FU, 5-fluorouracil; CI, continuous infusion.

Table 2
Grade 3/4 toxicity with intermittent bolus and infusional 5-FU/FA plus irinotecan used as adjuvant therapy (ACCORD 2) and first-line therapy for metastatic disease

Toxicity	Proportion of patients (%)	
	Adjuvant (ACCORD 2) [16]	First-line metastatic [13] ($n = 145$)
Neutropenia	28	46
Febrile neutropenia	3	3
Diarrhoea	12	13

Other trials investigating the role of irinotecan in adjuvant therapy include: CALGB C89803, which is comparing bolus 5-FU/FA with or without irinotecan in stage III disease; and a French study assessing the benefits of intermittent bolus and infusional 5-FU plus irinotecan, compared with bolus and/or infusional 5-FU/FA in stage II and III rectal cancer.

3.2. Irinotecan plus capecitabine

Capecitabine offers a way of achieving prolonged delivery of fluoropyrimidine therapy directly to the tumour by means of oral administration [17]. The potential benefits on patient quality of life have made this an attractive treatment option (Table 1). The QUASAR II trial was designed to investigate the benefits of combining irinotecan with capecitabine as adjuvant therapy compared with standard bolus 5-FU/FA. In the original trial design, patients with stage III disease were randomised to receive six months of treatment with bolus

5-FU/FA or capecitabine plus irinotecan. Following the publication of results from a randomised phase III study showing the efficacy of the vascular endothelial growth factor (VEGF)-directed monoclonal antibody, bevacizumab, in combination with 5-FU, FA and irinotecan in metastatic colorectal cancer [18] a third arm, capecitabine/irinotecan/bevacizumab, was added to the study. The main endpoints of the study, which aims to recruit 1250 patients to each arm, are three-year disease-free survival, overall survival and safety. The first efficacy results are expected in 2008.

4. Oxaliplatin plus 5-FU/FA

The phase III MOSAIC trial is comparing 5-FU (400 mg/m^2 bolus and 600 mg/m^2 22-h CI)/FA (200 mg/m^2) administered days 1 and 2 every 2 weeks with FOLFOX4 (5-FU/FA at the same dose as in the other arm plus oxaliplatin 85 mg/m^2 day 1) [19]. Altogether, 2248 patients with resected stage II (40%) or stage III (60%) colon cancer were enrolled. As of May 2003, preliminary results [20] showed that oxaliplatin significantly improved the three-year disease-free survival rate of all patients compared with 5-FU/FA alone (78% versus 73%, hazard ratio 0.77, $P < 0.01$). Survival data are not yet available. In addition, long-term neurotoxicity is a potential concern with this combination: grade 3 sensory neuropathy was observed in 12% of patients and was still evident in 1% of patients at one-year follow-up.

The addition of oxaliplatin to 5-FU/FA is also being investigated in a phase III trial by the National Surgical Breast and Bowel Project (NSABP) [21]. As with the MOSAIC trial, this trial includes both stage II and stage III colon cancer patients. However, the NSABP trial used bolus, compared with intermittent bolus and infusional, 5-FU/FA in the MOSAIC trial. A total of 2492 patients were randomised to receive bolus 3 eight-week cycles of 5-FU/FA alone (500/500 mg/m^2/week for 6 weeks) or in combination with oxaliplatin (85 mg/m^2 on weeks 1, 3 and 5 of each cycle). Preliminary safety results on 1852 patients revealed the occurrence of severe enteropathy in the form of (a) diarrhoea or severe dehydration with bowel wall injury and (b) grade 3/4 diarrhoea with grade 4 neutropenia or enteric sepsis: the frequencies of both (a) (5.9% versus 3.3%) and (b) (1.9% versus 0.6%) were higher in the oxaliplatin-based arm. As these events were not reported in the MOSAIC trial, it is tempting to speculate that they may be due, at least in part, to the bolus delivery of 5-FU/FA.

5. Stage II colorectal cancer

The benefits of adjuvant chemotherapy for patients with stage II colon cancer are still unclear [2]. A small benefit in a subpopulation of patients with stage II colon cancer is likely, but it is not clear how this can be defined. The concept of high-risk stage II colon cancer has been proposed [2], but this concept has not yet been validated. A pooled analysis of over 1000 patients with stage II (B) colon cancer who had undergone potentially curative resection failed to show a significant difference in event-free or overall survival between patients randomised to 5-FU/FA or to observation [22]. An analysis of data on over 3000 patients from a United States healthcare provider demonstrated that more than 25% of patients were given adjuvant chemotherapy, despite its uncertain benefits [23]. In this analysis, adjuvant chemotherapy did not improve patient survival: the five-year survival rate of patients not receiving adjuvant chemotherapy was 75%, compared with 78% for those receiving adjuvant chemotherapy.

The role of irinotecan-based adjuvant chemotherapy in stage II disease is currently being assessed in the PETACC-4 trial which compares the use of various infusional schedules of 5-FU/FA in combination with irinotecan, with surgery alone. Investigators can choose an experimental arm from one of the following: the FOLFIRI regimen (FA 400 mg/m^2 followed by 5-FU 400 mg/m^2 as an IV bolus and then 5-FU 2400 mg/m^2 as a 46 h continuous infusion in combination with irinotecan 180 mg/m^2 on day 1, administered every 2 weeks), the AIO regimen plus irinotecan (FA 500 mg/m^2 plus 5-FU/24 h 2000 mg/m^2 plus irinotecan 80 mg/m^2 $\times$ 6 weeks), or the TTD regimen plus irinotecan (irinotecan 80 mg/m^2 plus 5-FU/48 h infusion 2250 mg/m^2 weekly $\times$ 6 weeks). An important aspect is also the translational research in this study. Patients are stratified for treatment according to their microsatellite status. The study aims to recruit 1976 patients, making this the by far the largest trial of adjuvant therapy in patients with stage II disease.

6. Prognostic and predictive markers

There is no doubt that adjuvant chemotherapy prolongs the survival of many patients with stage III colon cancer. However, it is also acknowledged that adjuvant treatment may not be suitable for all patients and that the benefits of treatment must be weighed alongside the associated side effects. In order to optimise treatment, it should ideally be tailored to the individual patient. Prognostic and predictive factors, indicating those patients most likely to suffer disease recurrence and those most likely to respond to treatment, respectively, will be invaluable in identifying the patients most suitable for adjuvant therapy. As such, this approach is likely to be of particular value for patients with stage II disease. Marker identification is a rapidly expanding area of

research and a variety of potential prognostic and predictive candidates have been identified.

Prognostic markers include cell proliferation indices (Ki-67, Mib-1, proliferating cell nuclear antigen), oncogenes/tumour suppressor genes (p53, K-ras, Bcl-2, c-erbB2), microsatellite instability, angiogenesis markers (vascular endothelial growth factor), markers of invasion/metastasis (matrix metalloproteinases) and biochemical markers [thymidylate synthase (TS)]. The usefulness of these markers is still the subject of much investigation.

A number of predictive markers have been identified. The decoy receptor 3 (DcR3) gene is a negative regulator of Fas-mediated apoptosis. Amplification of this gene has been observed in colorectal tumours, where it is associated with no prognostic value but is an indicator of a poorer response to adjuvant chemotherapy than normal gene expression [24]. Microsatellite instability is another potentially useful predictive marker. A recent analysis showed that patients with stage II or III disease who had microsatellite stable tumours or tumours exhibiting only low microsatellite instability had a longer overall survival following 5-FU-based adjuvant chemotherapy than patients with tumours showing high frequency microsatellite instability [25]. The value of a particular marker will depend on the chemotherapy regimen being used. In advanced colorectal cancer, low gene expression levels of TS, dihydropyrimidine dehydrogenase (DPD) and thymidine phosphorylase (TP) are associated with response to 5-FU and survival [26]. Gene expression levels of topoisomerase I, p21 and bcl-2 may be predictive of a response to irinotecan.

Although some prognostic factors are also predictive of response to chemotherapy, and vice versa, this is not always the case. In a retrospective analysis of 431 patients, while TS, Ki67 and p53 were all useful prognostic markers, they were not predictive of a response to adjuvant chemotherapy [27].

Both the PETACC-3 and QUASAR-II trials, described earlier, have a translational research component. Identifying single nucleotide polymorphisms (SNPs) in enzymes involved in the metabolism of 5-FU, capecitabine and irinotecan will provide us with useful tools to determine the patients who will respond to treatment. This research will be combined with immunocytochemical studies on tumour tissue. Using these techniques, it is hoped to observe relationships between potential markers identified and patient outcome following chemotherapy.

7. Targeted agents for use in adjuvant chemotherapy

Targeted agents may offer a potential alternative to the traditional approach of cytotoxic chemotherapy for some patients. These have particular application in adjuvant disease due to their generally good tolerability profiles. Despite initially promising results, the monoclonal antibody, edrecolomab (which is directed against the cell-surface glycoprotein 17-1A) failed to show a survival benefit when added to 5-FU/FA [28]. The role of the VEGF-directed monoclonal antibody, bevacizumab, is currently being investigated in the QUASAR II study. Bevacizumab is well tolerated, with hypertension being the main side effect [18]. In addition, two phase III trials (VICTOR and PETACC-5) are assessing the efficacy of the cyclo-oxygenase inhibitors, rofecoxib and celecoxib, in addition to standard chemotherapy, in patients with resected stage II and III disease (VICTOR trial) and stage III (PETACC-5 trial).

8. Conclusions

Adjuvant chemotherapy prolongs the survival of at least some patients with stage III colon cancer, although its value in stage II disease is still uncertain. Until now, 5-FU/FA has formed the basis of chemotherapy. However, the introduction of newer, more active agents, such as irinotecan and oxaliplatin, may help to prolong the survival of patients, and randomised clinical trials are under way to determine the value of these agents. Targeted biological agents may offer an option to increase further the effects of traditional cytotoxic chemotherapy and their use is currently being investigated. Finally, tailoring therapy to the individual patient may be achieved to some extent by the identification of prognostic and predictive factors, which will help us to identify those patients whose disease is most likely to recur and to direct treatment to those most likely to respond to it.

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