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Irinotecan in combination with new agents

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Abstract

Today, irinotecan in combination with bolus and/or infusional 5-FU/FA constitutes a standard first-line treatment for patients with metastatic colorectal cancer. In an attempt to further improve clinical outcome, the use of irinotecan in combination with novel, targeted agents has been investigated. The theoretical attraction of combining irinotecan with targeted therapies is that this can improve the efficacy of treatment, but, due to the mainly non-overlapping toxicities of the agents involved, the toxicity of treatment should not be exacerbated. In this article we discuss recent data from clinical studies looking at the combinations of irinotecan with the 5-fluorouracil (5-FU) pro-drug, capecitabine, the cyclo-oxygenase (COX-2) inhibitor, celecoxib, and monoclonal antibodies against the epidermal growth factor receptor (cetuximab) and vascular endothelial growth factor (bevacizumab).

Keywords: Bevacizumab; Capecitabine; Celecoxib; Cetuximab; Colorectal cancer; Irinotecan

1. Introduction

Results from two pivotal phase III clinical trials have demonstrated that the addition of irinotecan to infusional or bolus 5-fluorouracil (5-FU)/folinic acid (FA) regimens significantly improves response rate, time to disease progression and median survival time [1,2]. More recently, irinotecan in combination with the high-dose infusional AIO 5-FU/FA regimen has also yielded encouraging results [3]. Irinotecan in combination with bolus or infusional 5-FU/FA constitutes a standard first-line therapy for patients with metastatic colorectal cancer. The activity of irinotecan in colorectal cancer has prompted its investigation in combination with agents other than 5-FU/FA [4]. The key to improving clinical outcome is to enhance efficacy without increasing the toxicity of treatment. Thus, much attention has been focused on combining irinotecan with specific, targeted agents that have no, or only partially overlapping, toxicities. In this article, we review the recent data for irinotecan in combination with capecitabine, the cyclo-oxygenase inhibitor, celecoxib, and the monoclonal antibodies bevacizumab and cetuximab, in the treatment of advanced and metastatic colorectal cancer.

2. Irinotecan plus capecitabine

Capecitabine is an orally active, fluoropyrimidine pro-drug which is converted enzymatically to 5-FU within tumour cells. Thus, capecitabine has the advantage not only of convenience of administration, which is attractive to patients, but also of being tumour-selective. Pooled data from two large, randomised, phase III trials

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involving over 1200 patients compared oral capecitabine (1250 mg/m^2 twice daily for 14 days every three weeks) with the Mayo Clinic 5-FU/FA regimen (5-FU 425 mg/m^2 plus FA 20 mg/m^2 days 1–5, every four weeks) as first-line treatment for metastatic colorectal cancer showed that capecitabine was associated with a significantly higher response rate (26% vs. 17%, $P < 0.0002$) and a similar time to disease progression, overall survival and duration of response compared with bolus 5-FU/FA [5]. Moreover, capecitabine demonstrated significantly less toxicity than bolus 5-FU/FA in terms of diarrhoea, stomatitis, nausea, alopecia and neutropenic fever/sepsis.

The combination of irinotecan and capecitabine has been investigated as first-line therapy in locally advanced and metastatic colorectal cancer. In a phase I study in 37 patients with metastatic disease, weekly administration of irinotecan (70 mg/m^2 for six weeks) in combination with capecitabine (2000 mg/m^2/day in a split dose for two weeks, starting on days 1 and 22) was found to be active, with a response rate of 38% [6]. Toxicity was manageable, with diarrhoea being the main side effect at this dose. Muñoz and colleagues reported the results of a study in which three-weekly administration of irinotecan (225 mg/m^2 (180 mg/m^2 if patients were over the age of 65 years)) in combination with capecitabine (2000 [1500] mg/m^2/day for two weeks, from days 2 to 15) was investigated in 56 patients with locally advanced or metastatic disease [7]. A median of three cycles of treatment were delivered, with a median relative dose intensity of 97% for both drugs. Treatment was well tolerated, even in older patients (⩾65 years), with the main toxicity being neutropenia/leukopenia. However, grade 3/4 diarrhoea and asthenia were reported in 7% and 4% of older patients, respectively, but in none of the younger patients, suggesting that dose reduction in such patients may be a consideration. Febrile neutropenia was seen in two patients (one cycle each) and there were two treatment-related deaths. The overall response rate among 42 evaluable patients was 45%, with two complete responses and 17 partial responses [7]. By October 2003, there were 67 evaluable patients, with a response rate of 46%, a tumour growth control rate of 81% and a time to progression of 7.4 months.

Borner and colleagues [8] compared the administration of irinotecan on a weekly (70 mg/m^2, days 1, 8, 15, 22 and 29) or a three-weekly (300/240 mg/m^2, days 1 and 22) basis in combination with capecitabine (2000 mg/m^2/day, days 1–14, 22–35, every 42 days) in a randomised phase II trial in metastatic colorectal cancer. A total of 75 patients entered the trial. Compared with three-weekly administration, weekly administration of irinotecan was associated with more grade 3/4 diarrhoea (32% vs. 19%), but less grade 3/4 neutropenia (5% vs. 19%) and less grade 2/3 alopecia (21% vs. 65%). Preliminary response rates were similar for both weekly and three-weekly irinotecan administration (42% and 41%). Time to progression was longer with the three-weekly (9.9 months) compared with weekly (7.2 months) administration. By October 2003, updated response data were markedly higher in the three-weekly administration group (35% vs. 18%), time to progression was essentially the same at 9.2 and 6.9 months (Fig. 1(a)) and the median overall survival was 24.7 months with the three-weekly regimen and 17.4 months with the weekly regimen (Fig. 1(b)).

Thus it appears that the combination of irinotecan and capecitabine is an active and well tolerated combination. Based on clinical findings showing a superiority of the three-weekly irinotecan regimen over the weekly regimen, the combination of three-weekly irinotecan with capecitabine is being investigated in further studies. One such study is European Organization for Research

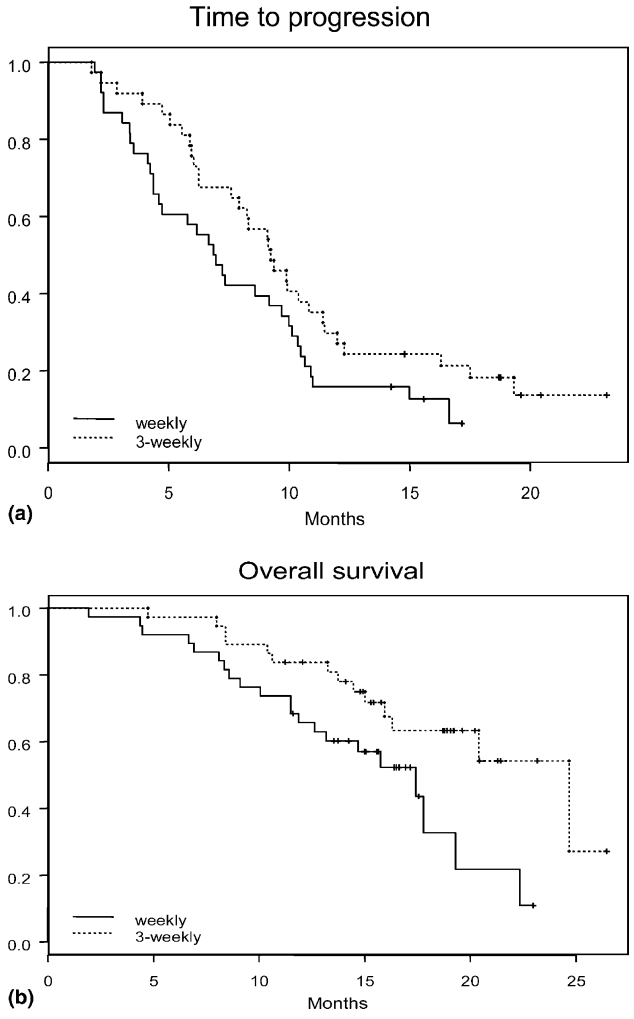

Fig. 1. (a) Progression-free and (b) overall survival in patients with locally advanced or metastatic colorectal cancer receiving a combination of capecitabine and irinotecan, administered either weekly or three-weekly.

and Treatment of Cancer (EORTC) 40015, a randomised phase III trial, in which irinotecan in combination with capecitabine (with or without celecoxib) is being compared with irinotecan in combination with 5-FU/FA (with or without celecoxib). This trial is described in further detail in the next section.

3. Irinotecan plus celecoxib

The cyclo-oxygenase (COX) enzyme, which converts arachidonic acid to prostaglandins, is expressed in two isoforms: COX-1, which is constitutively expressed, and COX-2, which is inducible in inflammation. A number of tumours express the COX-2 isoform, including breast [9,10], head and neck [11], cervical [12] and colorectal cancer [13–16], and COX-2 overexpression is generally an indicator of poor prognosis. In colorectal cancer, COX-2 may be involved in tumour progression via the modulation of angiogenesis and the proliferation of tumour cells, and interactions with other tumour promoting systems, such as vascular endothelial growth factor (VEGF) and the epidermal growth factor receptor (EGFR) have been suggested [15,16].

The non-steroidal anti-inflammatory drug, celecoxib, is a selective COX-2 inhibitor. Celecoxib has been shown to reduce the number of polyps in patients with familial adenomatous polyposis [17]. Preclinical studies have shown celecoxib to inhibit cell proliferation and to induce apoptosis in head and neck cancer cell lines [18]. In addition, celecoxib enhanced the cytotoxicity of a number of cytotoxic chemotherapeutic drugs, including 5-FU, doxorubicin, vincristine and bleomycin. Others, using murine models of colorectal cancer, have shown celecoxib to enhance the antitumour efficacy of irinotecan and reduce the severity of late onset diarrhoea in a dose-dependent manner [19].

The effects of combining celecoxib with irinotecan/5-FU/FA as first-line therapy in advanced colorectal cancer have recently been reported in two phase II trials, both of which administered chemotherapy as follows: irinotecan (125 mg/m^2), 5-FU (500 mg/m^2) and FA (20 mg/m^2) (IFL) weekly for four weeks, followed by a two-week rest; celecoxib (400 mg bid) was continued throughout the administration of IFL. Using this regimen, Blanke *et al*. reported a response rate of 28%, among 18 evaluable patients, with a further 56% of patients having stable disease [20]. The main grade 3/4 toxicity was neutropenia, which was reported in over two-thirds (39%) of 23 patients, two of whom also had fever. Non-haematological toxicity comprised mainly gastrointestinal effects, including grade 3/4 diarrhoea (22%) and grade 3/4 nausea (22%). Three patients experienced cardiovascular toxicity and there was one toxic death from a stroke, which was thought to be possibly related to treatment. In the second study, a Hoosier Oncology Group Study, patients also received oral glutamine (10 g tid) in addition to the IFL/celecoxib regimen described above [21,22]. At a median follow-up of 7.8 months in 31 evaluable patients, the response rate was 42%, with two complete and 11 partial responses. The one-year survival rate was 57%. There were no episodes of grade 4 diarrhoea reported, although 42% of patients had grade 3 diarrhoea. Thirty-four percent of patients had grade 3/4 neutropenia, but there were no reports of neutropenic fever. There were two treatment-related deaths (gastrointestinal bleeding/aspiration and a possible pulmonary embolism).

The benefits of adding celecoxib to irinotecan-based chemotherapy in metastatic colorectal cancer are now being investigated in a large multicentre, randomised phase III trial (EORTC 40015). Patients will receive either capecitabine (1000 mg/m^2 bid, days 1–14) plus irinotecan (250 mg/m^2, day 1) every 21 days, or biweekly infusional 5-FU/FA plus irinotecan (180 mg/m^2, day 1) every 14 days. Irinotecan is administered prior to capecitabine. In a two-by-two factorial design, patients will also be randomised to either placebo or celecoxib (400 mg bid). Seventy-nine centres are involved in this trial which has a target accrual of 692 patients. Recruitment began in May 2003 and is expected to continue until the end of 2007.

4. Irinotecan plus monoclonal antibodies

4.1. Irinotecan plus cetuximab

The EGFR is a cell membrane growth factor receptor which plays an important role in cell growth, differentiation and survival [23–25] and which is now thought to be central to the growth regulation of various tumours. The binding of activating ligands, such as epidermal growth factor (EGF) and transforming growth factor alpha (TGF-α), to the EGFR is followed by activation of intracellular tyrosine kinase domains. This leads to a variety of effects, such as the promotion of angiogenesis and the inhibition of apoptosis, which can lead to the development and progression of tumours. Many human tumours express high levels of EGFR, including CRC [26–28], in which it is an indicator of reduced survival [29]. Studies in metastatic colorectal cancer have shown levels of EGFR expression of 72% and 82% [28,30].

Cetuximab is a chimeric monoclonal antibody that targets the EGFR and competitively inhibits the binding of the natural ligands. This inhibits the activation of the signal transduction pathways that depend on tyrosine kinase activity. Cetuximab appears to potentiate the cytotoxic activity of irinotecan. In preclinical studies using established colorectal tumour xenografts, the addition of cetuximab to irinotecan improved the inhibition of tumour growth or tumour regression [31].

Activity of the cetuximab/irinotecan combination in irinotecan-refractory xenografts was also noted, whereas either agent alone did not control tumour growth. Despite the enhancement of irinotecan activity, clinical study has shown no pharmacokinetic interaction between irinotecan and cetuximab [32]. A number of clinical studies have now been conducted investigating the use of irinotecan in combination with cetuximab in EGFR-expressing advanced colorectal cancer (Table 1).

Initial studies investigated the use of cetuximab as second-line therapy in patients with EGFR-expressing disease refractory to both 5-FU and irinotecan. In an early study by Saltz *et al.* [30], the combination of irinotecan (at the same dose and schedule that patients had progressed on) with cetuximab (400 mg/m^2 loading dose followed by 250 mg/m^2 weekly) led to a response rate of 17% in 21 patients. In a subsequent study by the same group, the use of cetuximab alone (at the same dose as described above) in irinotecan-refractory disease was associated with a response rate of 11% [33]. The main toxicity associated with cetuximab is an acne-like skin rash, which was seen in 61% of patients in the early study and in 86% in the subsequent study. This rash does not appear to compromise continued treatment.

Following on from these two non-randomised studies, a phase II randomised study comparing cetuximab alone or in combination with irinotecan in patients with irinotecan-refractory EGFR-expressing metastatic colorectal cancer was carried out [28]. Patients were randomised to receive cetuximab (400 mg/m^2 loading dose followed by 250 mg/m^2 weekly) either alone ($n = 111$) or in combination with irinotecan (at the same dose and schedule on which patients had progressed) ($n = 218$). Many patients were heavily pretreated, nearly half (45%) having received three or more previous lines of therapy. The combination of irinotecan and cetuximab gave a higher response rate (23% vs. 11%, $P = 0.0074$), better tumour growth control (56% vs. 32%, $P = 0.0001$) and a longer time to disease progression (4.1 months vs. 1.5 months, $P < 0.0001$) than cetuximab alone. The results are particularly encouraging in view of the relatively large number of patients who had received three or more previous lines of therapy. There was no correlation between the degree of EGFR expression and the response to therapy. However, there was some evidence of a link between the development of skin toxicity and efficacy: patients receiving the irinotecan/cetuximab combination who had any skin reaction had a better response rate (26% vs. 6%) and a longer survival (median 9.1 vs. 3 months) than those with no skin reaction [28].

Three phase II studies have now shown promising activity of the combination of cetuximab, irinotecan and different regimens of bolus and/or infusional 5-FU/FA as first-line therapy for EGFR-expressing metastatic colorectal cancer [34–36]. In a study reported by Van Laethem *et al.* [35] weekly cetuximab (400 mg/m^2 loading dose followed by 250 mg/m^2 weekly) was combined with bi-weekly irinotecan (180 mg/m^2), FA (400 mg/m^2) and bolus 5-FU followed by an infusion of either high-dose (2400 mg/m^2 46-h infusion) or low-dose (2000 mg/m^2, 46-h infusion) 5-FU. Over the two groups, 12 of 18 patients (67%) had a partial response, and 22% had stable disease [35]. By October 2003, updated information showed that out of 22 patients, the response rate was 59%, with a further 36% of patients with stable disease, giving a tumour growth control rate of 95%. In addition, following chemotherapy seven patients were able to undergo R0 resection for hepatic or lung metastases. There was no difference in the response rate

Table 1
Irinotecan, alone or together with bolus and/or infusional 5-FU/FA, combined with cetuximab in the treatment of patients with previously treated or untreated EGFR-expressing metastatic colorectal cancer

Line of therapy	Study type	Treatment	*N*	Response rate	
				PR (%)	TGC (%)
Second- or subsequent-line for irinotecan-refractory disease	Non-randomised [30]	Cetuximab + irinotecan at the same dose and schedule that disease progressed on	121	17	48
	Non-randomised [33]	Single-agent cetuximab	57	11	33
	Randomised [28]	Cetuximab + irinotecan at the same dose and schedule that disease progressed on vs.	218	23	56
		Single-agent cetuximab	111	11	32
First-line	Non-randomised [34]	Cetuximab + irinotecan/bolus and infusional 5-FU/FA[†]	13	38	46
First-line	Non-randomised [36]	Cetuximab + irinotecan/bolus 5-FU/FA	25	44	64
First-line	Non-randomised [35]	Cetuximab + irinotecan/bolus and infusional 5-FU/FA	22	59	95
		High-dose 5-FU group vs.	12	58	100
		Low-dose 5-FU group	10	60	90

See text for details of doses. [†]Preliminary data. *N*, number of patients; PR, partial response; TGC, tumour growth control.

between the high- and low-dose 5-FU groups, but the tumour growth control rate was higher in the high-dose 5-FU group (100% vs. 90%). In the high-dose 5-FU group, diarrhoea was markedly higher than in the low-dose group (28% vs. 0%) and there were three dose-limiting toxicities compared with none in the low-dose group.

The results from these studies show that the combination of irinotecan and cetuximab is well tolerated and demonstrates significant clinical activity in patients with heavily pre-treated advanced colorectal cancer. Significantly, this combination was highly active in patients whose disease had progressed on irinotecan as the last treatment prior to randomisation, indicating that this combination is able to re-establish the irinotecan-sensitivity of the disease. Whether or not this is an agent-specific finding remains to be clarified. In addition, irinotecan/5-FU/FA plus cetuximab is well tolerated and very active as first-line therapy and further clinical trials are expected to establish the role of this combination in the first-line setting. Randomised phase III studies are required to assess the impact on survival of adding cetuximab to chemotherapy.

4.2. Irinotecan plus bevacizumab

Tumour angiogenesis is necessary for tumour growth, progression and metastasis. VEGF, which promotes angiogenesis by binding to receptors on the vascular endothelium, is a critical growth factor for tumour angiogenesis. In a review of 35 studies between 1996 and 2001, VEGF levels were reported to be high in a number of tumour types, including colorectal cancer [37]. High levels of VEGF expression are associated with a significantly poorer overall survival than low levels [38].

Bevacizumab is a recombinant humanised monoclonal antibody directed against VEGF. A recent randomised phase II trial in metastatic colorectal cancer showed that the addition of bevacizumab (5 mg/kg every two weeks) to bolus 5-FU/FA led to a higher response rate (40% vs. 17%), a longer median time to disease progression (9.0 vs. 5.2 months), and a longer median overall survival (21.5 vs. 13.8 months) [39]. Thrombosis was the most significant adverse event and was responsible for one patient death. Other toxicities of concern were proteinuria and epistaxis.

The benefit of adding bevacizumab to first-line irinotecan-based chemotherapy for advanced disease was recently shown in a phase II trial [40] and a large randomised phase III trial [41]. In the phase III trial, patients were randomised to receive either IFL (irinotecan 125 mg/m^2, bolus 5-FU 500 mg/m^2, FA 20 mg/m^2) plus placebo or IFL plus bevacizumab (5 mg/kg every two weeks). These formed the primary comparison groups. A further group of patients received 5-FU (500 mg/m^2)/FA (500 mg/m^2) plus bevacizumab. At the time of disease progression, patients were unblinded and able to continue bevacizumab in combination with second-line therapy. In the primary comparison groups, the addition of bevacizumab to IFL ($n = 403$) resulted in a significantly improved response rate (45% vs. 35%, $P = 0.0029$) and an increase in the duration of response of almost 50% (10.4 vs. 7.1 months, $P = 0.0014$) (Fig. 2). In addition, IFL plus bevacizumab was associated with a longer progression-free survival (10.6 vs. 6.24 months, $P < 0.00001$) and a 30% increase in the median survival (20.3 vs. 15.6 months, $P = 0.00003$) compared with IFL/placebo ($n = 412$). In terms of toxicity profile, in the phase II study, there were nine thrombotic events, eight of which were grade 3/4 [40]. In the phase III study, only hypertension was found to be significantly increased in patients receiving bevacizumab (22.4% vs. 8.3%, $P < 0.01$) [41]. This was easily managed with oral medication. There was also some evidence that gastrointestinal perforations, although rare, could be increased by the addition of bevacizumab to IFL (1.5% vs. 0.0%) [41]. The results from the phase III study are remarkable because of the large number of patients involved in the study (which underline the reliability of the data) and the 30% increase in median overall survival, which is particularly impressive in this patient group. In addition, the combination of bevacizumab and IFL has only a limited cost in terms of toxicity. Combinations of bevacizumab with infusional 5-FU/FA and either irinotecan or oxaliplatin are currently under investigation.

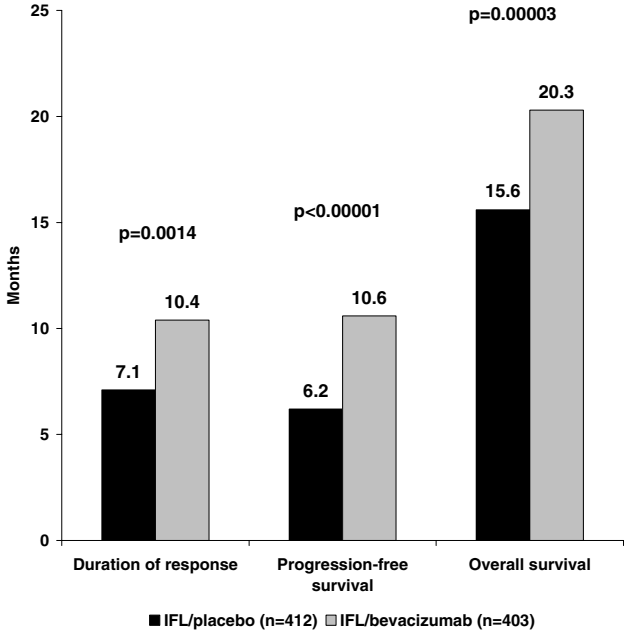

Fig. 2. Median response duration, progression-free and overall survival of patients with metastatic colorectal cancer receiving irinotecan/bolus 5-FU/FA in combination with bevacizumab. Results from a randomised phase III trial [41]. IFL, irinotecan, 5-fluorouracil, folinic acid.

5. Conclusions

The combination of irinotecan with bolus and/or infusional 5-FU/FA constitutes a standard first-line treatment for metastatic colorectal cancer. However, the aim is to further improve patient outcome and to reduce treatment-related side effects. The results of studies discussed here show that combining irinotecan with targeted therapies can improve outcome in terms that matter to patients, which is by prolonging survival without increasing the side effects associated with treatment.

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