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Current Status of Colorectal Cancer: CPT-11 (Irinotecan), a Therapeutic Innovation

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Colorectal cancer affects around 5% of the population in Westernised countries and is associated with a high level of morbidity and mortality. Overall, around 50% of patients can expect to be fully cured by surgery, along with recent improvements in survival due to the use of adjuvant therapy. However, in patients who develop metastatic disease, the prognosis is poor, and the appropriateness of anticancer chemotherapy in such patients has been controversial. Nevertheless, there is increasing evidence that chemotherapy can extend life expectancy in colorectal cancer and that in metastatic disease patients achieve a significant benefit from early rather than late chemotherapy. For first-line treatment of metastatic colorectal cancer, the best available regimens have been those which include 5-fluorouracil (5-FU) and folinic acid; a meta-analysis of nine randomised clinical studies of such regimens produced a mean response rate of 23%. However, in those who fail or relapse, there has been no established second-line alternative. The development of CPT-11 (Campto®, irinotecan), a specific inhibitor of topoisomerase I, represents a significant advance in the management of colorectal cancer. Following encouraging observations of sustained activity in colon cancer cell lines, including those having the MDR phenotype, clinical studies of CPT-11 monotherapy in both chemotherapy-naive and pretreated patients with advanced colorectal cancer demonstrated response rates at least equivalent to those achieved with first-line 5-FU/folinic acid combination therapy. This indicates that CPT-11 does not exhibit cross-resistance with 5-FU, making it the first effective second-line agent in this setting. Further studies are ongoing to define the optimum dosage schedule for CPT-11 and to assess the utility of CPT-11 as a single agent in second-line therapy, or combined with 5-FU and other anticancer agents as first-line therapy. In conclusion, CPT-11 offers a different cytotoxic approach that may complement the use of 5-FU/folinic acid in colorectal cancer in the future.

Key words: CPT-11 (irrinotecan), colorectal cancer, topoisomerase I inhibitor, MDR phenotype

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INTRODUCTION

COLORECTAL CANCER is one of the most common cancers in the developed world, affecting approximately 1 person in 20 in the United States and most other Westernised countries [1]. This malignancy is curable by surgical treatment if diagnosed in its early stages. However, approximately 50% of patients who have undergone surgery will eventually die of metastatic disease [2]. Adjuvant chemotherapy has been used and studied in clinical trials since the late 1950s, but has produced variable results [1]. Perhaps as a result of the combined effects of improved understanding of the disease, earlier diagnosis, and attempts to optimise surgical techniques and adjuvant therapies, the 5-year survival rate increased between the 1950s and the 1980s from 41% to 54% for colon cancer and from 40% to 51.5% for rectal cancer [1]. Nevertheless, these figures demonstrate a need to develop therapies which will improve the control of metastatic disease.

In the past, the use of chemotherapy for the treatment of metastatic disease has been controversial, with 5-fluorouracil (5-FU) monotherapy producing response rates of less than 20%. However, colorectal cancer is now attracting much more attention from the medical oncology community, and there is growing evidence to suggest that appropriate chemotherapy with 5-FU is effective in extending the life expectancy of patients with this disease.

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AVAILABLE CHEMOTHERAPY FOR COLORECTAL CANCER

Adjuvant therapy

Evidence that the life expectancy of patients with colorectal cancer can be extended with certain chemotherapy regimens is provided by two recently completed key studies (Table 1) [3, 4]. A recently published pivotal study has shown that a combination of 5-FU and levamisole used as adjuvant chemotherapy in Dukes' C colon cancer has a significant impact on the survival of these patients [3]. After a median follow-up of 6.5 years (range 4–7.5), there were 121 cancer deaths among 304 patients treated with 5-FU/levamisole plus surgery, compared with 168 deaths in 315 patients who were treated by surgery alone. This represented a highly significant ($P = 0.0007$) reduction in cancer-related deaths of 33% with the use of adjuvant 5-FU/levamisole chemotherapy.

A survival benefit has also been demonstrated with the use of 5-FU/folinic acid adjuvant chemotherapy. In the IMPACT (International Multicentre Pooled Analysis of Colon Cancer Trials) study [4], patients with Dukes' B and C colon cancer were randomised to adjuvant chemotherapy with a folinic acid-modulated regimen of 5-FU (given as a 5-day intravenous bolus schedule) ($n = 754$), or control (surgery alone) ($n = 772$). This study demonstrated that, overall, the difference in survival rates in patients who received adjuvant 5-FU/folinic acid compared with those who had surgery alone was statistically significant ($P = 0.029$). Subgroup analyses revealed that this survival benefit occurred only in patients with Dukes' C colon cancer—in this group, 3-year survival rates were 76% and 64% in the chemotherapy and control groups, respectivel However, in patients with Dukes' B disease, the differen in survival rates between patients who received adjuva chemotherapy and those treated with surgery alone was n statistically significant. Indeed, it has been suggested th among patients with Dukes' B colon cancer, there is a ne to identify the higher-risk patients as those who will bene from 5-FU/folinic acid adjuvant chemotherapy.

In the ongoing NSABP (National Surgical Adjuva Breast and Bowel Project) C04 study, the impact on sur val of three 5-FU-based adjuvant regimens is being cor pared [38]. 2151 patients with Dukes' B or C col cancer were randomised between July 1989 and Decemb 1990 to 12 months' chemotherapy with 5-FU/folinic ac with or without levamisole, or the classical 5-FU/levamis regimen of Moertel and associates [3]. So far, after a n dian follow-up of 4.5 years, there appears to be no sign cant difference between the three regimens in terms relapse rates and survival, indicating that 5-FU/levamis is equivalent to 5-FU/folinic acid, and that addition levamisole to 5-FU/folinic acid produced no additio benefit.

Although the results of several other recently comple trials are awaited, the growing consensus is that the role levamisole in the adjuvant treatment of colorectal cancer decreasing and that 5-FU/folinic acid is the preferred co bination.

Two other NSABP trials have investigated the impact 5-FU-based adjuvant chemotherapy on survival in patie with Dukes' B and C colon cancer. In the NSABP C study, adjuvant methyl-CCNU/vincristine/5-FU (MO

Table 1. Key studies that show the effect of adjuvant chemotherapy on survival in patients with advanced (Dukes' stage B2 or colorectal cancer

[Ref.]	Number of patients	Adjuvant chemotherapy			Median follow-up	Impact on surviv
		5-Fluorouracil	Levamisole	Folinic acid		
[3]	304	✓ 450 mg/m^2 i.v. daily, d1–5, then weekly (starting d28)	✓ 50 mg p.o. tds for 3d, q2w for 1 year	–	6.5 years	Significant reduction in mortality with 5-FU/levamisole versus surgery alone (reduction c 33%; $P = 0.0007$)
	310	–	✓ 50 mg p.o. tds for 3d, q2w for 1 year	–		
	315	None	None	None		
	754	✓ 370–400 mg/m^2 i.v. daily for 5d q28d × six cycles	–	✓ 200 mg/m^2 daily for 5d q28d × six cycles	37 months	3-year survival rates, chemotherapy versus surgery alone: 76% versus 64% (Dukes' C); 88% versus 90% (Dukes' B); 83% versus 78% (overall; $P = 0.029$
	772	None	None	None		

i.v., intravenous bolus injection; d, day(s); p.o., orally; tds, three times a day; q2w, every 2 weeks; q28d, every 28 days.

produced a small but statistically significant increase in 3-year survival versus control (surgery alone) (75% versus 72%; $P = 0.05$) [5]. Because of this survival benefit, a further study was performed to compare the MOF regimen with 5-FU plus folinic acid (NSABP C03). A further significant survival advantage was demonstrated with the latter regimen over MOF (84% versus 77%; $P = 0.003$). Considering the two studies together, the survival rates observed in the two MOF-treated groups are very similar, and the comparison between the 5-FU/folinic acid group in NSABP C03 and the control group (surgery alone) in NSABP C01 produces a 12% absolute survival advantage. In these NSABP trials, the benefit is independent of Dukes' stage. These results are similar to those obtained in patients with Dukes' C disease given a similar regimen in the IMPACT study [4].

As already described, the results of the adjuvant studies showed that patients with more advanced disease (Dukes' C) clearly benefit from adjuvant chemotherapy. However, it is important to identify patients with Dukes' B tumours who are at high risk of failing primary therapy and, therefore, develop recurrent or metastatic disease. To this end, Johnston and colleagues [6] investigated thymidylate synthase (TS) expression in 294 patients treated for rectal cancer with adjuvant MOF, who were among those enrolled in the NSABP R-01 protocol. TS levels in the primary tumour were assessed along side the clinical outcome of the patients. The overall 5-year survival rate in patients with tumours that had a low expression of TS ($n = 91$) was significantly higher than those with tumours of high TS intensity ($n = 203$) (60% versus 40%; $P = 0.01$). Analysis of the effect of chemotherapy by TS status revealed that adjuvant chemotherapy of rectal cancer had a very significant impact in patients with high TS intensity tumours, increasing 5-year survival from 31% with surgery alone to 54% ($P < 0.01$). There appeared to be no benefit in low-intensity tumours (survival rates 57% versus 50% in MOF versus control group; ns).

Other important prognostic factors in Dukes' B tumours include lymphatic, neural or vascular (extra-mural) invasion and loss of the *DCC* and *TP53* genes. Eventually, it should be possible to identify the high risk patients using this constellation of parameters and this will maximise the benefit of adjuvant chemotherapy.

Metastatic disease

Within Europe, there are considerable variations in attitudes towards the treatment of metastatic colorectal cancer, and the definitive role of chemotherapy in these patients remains controversial, although less so than before. Since its introduction in 1957, 5-FU remains the most widely used cytotoxic agent in this setting. A wide range (8–85%) of response rates has been reported, probably reflecting varying factors such as patient selection criteria, disease severity, metastatic sites, previous therapy and, importantly, the intensity of 5-FU administration [1]. However, response rates following 5-FU monotherapy in patients with metastatic colorectal cancer do not usually exceed 20%. Attempts to improve the therapeutic benefit of 5-FU have included modifications of administration route and schedule, and the use of concomitant cytotoxic agents (reviewed below), but few studies have demonstrated an improvement in survival.

Nevertheless, a small study reported by Scheithauer and colleagues [7] provides important evidence in support of the use of chemotherapy in metastatic colorectal cancer. Patients who received 5-FU/folinic acid/cisplatin ($n = 24$), lived almost twice as long as those given best supportive care alone (median 11 versus 5 months; $P < 0.006$). Furthermore, quality of life was maintained in the chemotherapy-treated patients.

When to treat?

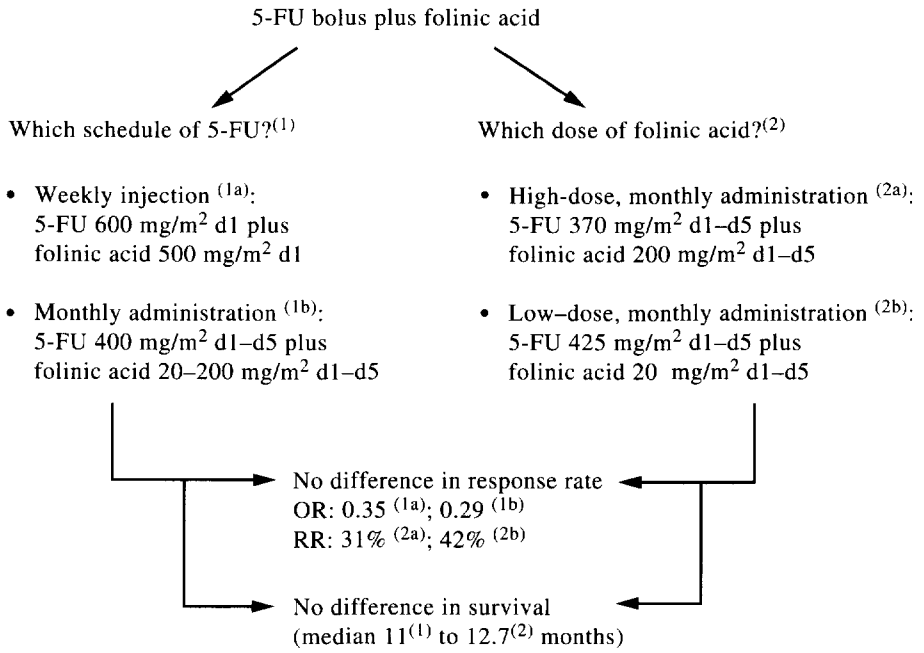
The optimal time for initiating chemotherapy in patients with metastatic colorectal cancer is an important issue for discussion: should we treat patients with early, asymptomatic disease, or wait until the patient develops symptoms? An important study from the Nordic Group [8] demonstrated a significant benefit for early treatment versus late treatment. Patients with advanced colorectal cancer were randomised between early chemotherapy (initiated before the emergence of symptoms; $n = 92$) and later chemotherapy (deferred until symptoms developed; $n = 91$). Chemotherapy in both groups comprised 12 courses of 5-FU (500 mg/m^2 as an intravenous bolus at 3 and 23 h every 2 weeks), methotrexate (250 mg/m^2 as a 2-h intravenous infusion every 2 weeks for the first eight courses, then every 4 weeks) and folinic acid rescue. The median survival was longest in the early-treatment group (14 versus 9 months); in addition, early chemotherapy was associated with a longer symptom-free period (median 10 versus 2 months). These results indicate that it is best to treat at the stage of lowest tumour burden.

Which regimen?

There is a great deal of debate about the optimal chemotherapy regimen for advanced colorectal cancer. It is generally agreed that first-line therapy should involve a 5-FU-based regimen. Indeed, attempts to improve outcomes in colorectal cancer have focused on enhancing the therapeutic efficacy of 5-FU while avoiding higher systemic doses which lead to unacceptably high levels of toxicity. Such strategies have been reviewed in detail by Cohen and associates [1] and have included the use of modulating agents such as folinic acid, methotrexate or interferon, the use of prolonged or continuous infusions of 5-FU rather than the standard intravenous bolus schedule, and the use of regional infusion techniques.

The most successful approach to modulating 5-FU activity has been its combination with folinic acid. A meta-analysis of nine randomised clinical trials that compared 5-FU with 5-FU/folinic acid in patients with metastatic colorectal cancer [9] confirmed what was apparent from randomised and non-randomised studies—that the response rate to 5-FU/folinic acid ($n = 803$) is, on average, double that of 5-FU alone ($n = 578$) (23% versus 11%; $P < 10^{-7}$). However, the survival curves of the two groups in this analysis were superimposible, perhaps because patients are likely to have changed to 5-FU/folinic acid therapy if they had failed to respond to 5-FU alone.

There are many different schedules of 5-FU/folinic acid currently used throughout Europe and North America. The North Central Cancer Treatment Group (NCCTG) regi-



1. Advanced Colorectal Cancer Meta-Analysis Project 1992 [9].
2. Poon et al. 1991 [10].

d, day(s); OR, odds ratio; RR, response rate.

Figure 1. Comparison of different schedules of 5-FU plus folinic acid in patients with metastatic colorectal cancer.

men is the most widely used of these and comprises intravenous bolus injections of 5-FU 425 mg/m² plus low-dose folinic acid, each given daily for 5 consecutive days, repeated every 4 weeks. Randomised comparisons between this and various other schedules, including a higher-dose folinic acid schedule and a weekly 5-FU/folinic acid schedule, have shown no major differences in response rates (Figure 1) [9, 10]. These observations have been confirmed in a recent prospective randomised study comparing seven different 5-FU-based regimens in a total of 589 eligible patients with advanced colorectal cancer (Table 2) [11]. Given that efficacy is equivalent between different dosage regimens, the use of lower dosages of folinic acid is likely to have economic advantages in terms of lower drug costs. Furthermore, randomised studies comparing high-dose and low-dose folinic acid schedules (Figure 1) have shown the lower dose results in fewer days in hospital associated with drug-related toxicity. This is important not only from an economic perspective, but also in terms of the impact on patients' quality of life. Nevertheless, severe stomatitis still occurs in up to one-third of patients treated with bolus 5-FU plus folinic acid [10], and leucopenia and severe diarrhoea each occur in up to 20% (Table 3) [7, 10]. Hospitalisation is necessary in 6.5–15% of patients on this regimen [10], and the average toxic death rate is 2.5% [12].

After 5-FU failure or relapse (a patient who has been treated with optimally modulated 5-FU or with one of the 5-FU infusional schedules), there are no accepted standard second-line therapies with established efficacy. New studies are required in this setting to investigate the efficacy and safety of combinations of 5-FU with other agents, high-dose 5-FU schedules and chronomodulation of 5-FU, although to date, patients who have failed to respond to first-line 5-FU-based chemotherapy have seldom responded to subsequent 5-FU-based regimens administered as a different dose or schedule or with a different modulating agent [1]. The development of new anticancer drugs with activity against colorectal cancer is, therefore, particularly important.

CPT-11, A NOVEL AGENT FOR THE TREATMENT OF COLORECTAL CARCINOMA

CPT-11 (Campto®, irinotecan) is a semisynthetic water-soluble derivative of camptothecin, a plant alkaloid which has demonstrated significant activity against experimental tumour models [13, 14]. CPT-11 is rapidly esterified *in vivo* to SN-38, an active metabolite that contributes significantly to the antitumour activity of the drug [15, 16]. Indeed, among camptothecin derivatives, SN-38 has demonstrated the most potent antitumour activity *in vitro* to date [17]. The mechanism by which CPT-11 and other camptothecin derivatives exert their antitumour activity is unique among anticancer agents. CPT-11 inhibits the nuclear enzyme DNA-topoisomerase I, leading to lethal accumulation of single-strand DNA breaks in the cell by inter-

Table 2. Comparison of the efficacy of various regimens of 5-fluorouracil (5-FU) compared prospectively in a study of 589 eligible patients with advanced colorectal cancer (adapted from Leichman et al. [11])

Schedule	1	2	3	4	5	6	7
Number of patients assessable for efficacy	60	61	60	61	58	63	63
Confirmed objective response rate (CR + PR)	24%	17%	14%	18%	17%	15%	13%
Median survival time (months)	14	14	13	15	14	15	11

CI, continuous infusion; CR, complete response; i.v., intravenous; PALA, phosphonacetyl-L-aspartate; PR, partial response.
Dosage schedules: 1: 5-FU 500 mg/m^2 i.v. bolus, days 1–5 every 5 weeks; 2: 5-FU 425 mg/m^2 i.v. bolus, days 1–5 every 4 weeks for two cycles, then every 5 weeks, plus folinic acid 20 mg/m^2 i.v. bolus, day 1 of each cycle; 3: 5-FU 600 mg/m^2 i.v. bolus weekly for 6 weeks then 2-week break, plus folinic acid 500 mg/m^2 3 h infusion, day 1 of each 8-week cycle; 4: 5-FU 300 mg/m^2/day CI, days 1–28, then 1-week break; 5: 5-FU 200 mg/m^2/day CI, days 1–28, then 1-week break, plus folinic acid 20 mg/m^2 i.v. bolus, days 1, 8, 15 and 22 of each 5-week cycle; 6: 5-FU 2600 mg/m^2 24-h infusion weekly (no breaks); 7: 5-FU 2600 mg/m^2 24 h infusion weekly plus PALA 250 mg/m^2 over 15 min, 24 h before each 5-FU infusion.

fering with the relaxation and recombination of supercoiled DNA and the transcription and translation of genetic material [15, 18].

Preclinical studies in human tumours have indicated that CPT-11 has activity against a broad range of tumours, including mesothelioma, non-small cell lung cancer, ovarian cancer and colorectal cancer, which are classically regarded as being resistant to cytotoxic chemotherapy [19]. This activity has been demonstrated even in tumour cell lines that express multidrug resistance (MDR), a phenotype that is particularly prevalent in colon cancer cells [20, 21].

The activity of CPT-11 in cancers which do not normally respond well to chemotherapy has been confirmed in clinical studies in Europe and Japan (Table 4) [22–31]. Even in intractable non-Hodgkin's lymphoma, 42% of evaluable patients show a response to a weekly cycle of CPT-11 40 mg/m^2 daily for 3 days, including 15% with complete responses.

However, it is in colorectal cancer that CPT-11 has shown greatest potential to date. The rationale behind using CPT-11 in colorectal cancer is based on the following key factors:

- Topoisomerase I levels are up to 14- to 16-fold higher in colon cancer cells than in normal tissue, suggesting that this enzyme may be an important target in the treatment of colorectal cancer [32]. Furthermore, high concentrations of topoisomerase I are present in both proliferating and quiescent cells; therefore, topoisomerase I inhibitors, such as CPT-11, are likely to be active in slowly- as well as rapidly-proliferating tumours [33].
- Colorectal cancer cells have been shown to express high levels of the P-glycoprotein-mediated MDR phenotype, a key mechanism of tumour resistance to anticancer chemotherapy [34], and this may explain why so few anticancer agents have demonstrated significant activity in this disease. However, the antitumour activity of CPT-11 has been evident even in tumours that express the *MDR* gene. In particular, a very low level of resistance to CPT-11 is seen in human tumour cell lines that are resistant to colchicine, vinblastine, vincristine or doxorubicin (Figure 2) [20, 21].

Table 3. Toxicity profile of regimens of 5-FU bolus plus folinic acid in metastatic colorectal cancer

Adverse event	Incidence in clinical trials (% of patients)
Severe stomatitis [10]	28
Severe diarrhoea [10]	16–19
Leucopenia [7] (WBC $<2 \times 10^9$/l)	15–22
Hospitalisation [10]	6.5–15
Toxic death [12]	2.5

WBC, white blood cell count.

Clinical experience with CPT-11 in colorectal cancer

The encouraging findings from preclinical studies of CPT-11 are supported by the results obtained in clinical trials in colorectal cancer. In phase II studies in 360 assessable patients with advanced colorectal cancer, CPT-11 100–150 mg/m^2 weekly or bi-weekly (Japan, U.S.) or 350 mg/m^2 every 3 weeks (Europe) produced overall objective response rates ranging from 18 to 31% and a median duration of response of approximately 7–9 months (pages S13–S17). These results are comparable to those achieved with 5-FU plus folinic acid. Even in patients who had received prior chemotherapy for advanced disease, response rates of 15–22% and response durations of approximately 6–8 months were achieved. Indeed, the activity of CPT-11 in patients refractory to 5-FU represents a significant advance in the treatment of colorectal cancer, as this suggests no cross-resistance with 5-FU. Therefore, it is the first effective second-line agent in this setting.

As 5-FU is the most active established agent for the treatment of colorectal cancer, and CPT-11 represents a different cytotoxic approach, it is logical to combine these two drugs in an attempt to improve further on the results obtained with CPT-11 monotherapy. Various administration schedules of CPT-11/5-FU combinations have already been investigated in phase I studies in Japan, the

Table 4. Summary of phase II studies of CPT-11 in tumours other than colorectal cancer, demonstrating a wide spectrum of anticancer

Tumour type and treatment stage	CPT-11 dosage	Number of evaluable patients	Response rate	[Ref.]
European studies				
NSCLC (first-line)	350 mg/m^2 q3w	15	27%	[22]
Cervix (first-line)	350 mg/m^2 q3w	21	24%	[23]
Pancreas (first-line)	350 mg/m^2 q3w	32	9%	[24]
Japanese studies				
NSCLC (first-line)	100 mg/m^2 weekly	72	32%	[25]
SCLC (first- or second-line)	100 mg/m^2 weekly	35	37%	[26]
SCLC (second-line)	100 mg/m^2 weekly	15	47%	[27]
Cervix (first-line)	100 mg/m^2 weekly or 150 mg/m^2 q2w	55	24%	[28]
Ovary (second-line)	100 mg/m^2 weekly or 150 mg/m^2 q2w	52	23%	[29]
Stomach (first- or second-line)	100 mg/m^2 weekly or 150 mg/m^2 q2w	60	23%	[30]
Pancreas (first- or second-line)	100 mg/m^2 weekly or 150 mg/m^2 q2w	62	42%	[31]
NHL (second-line)	40 mg/m^2 daily for 3d, weekly	62	42%	[39]

q, every; w, weeks; NSCLC, non-small cell lung cancer; NHL, non-Hodgkin's lymphoma.

U.S. and Europe, and these have been reviewed by Saltz and colleagues (pages S24–S31). Preliminary results indicate that concurrent administration of substantial doses of CPT-11, 5-FU and folinic acid is feasible in terms of safety. Furthermore, there appears to be no pharmacokinetic interaction between the drugs, and some evidence of clinical activity has been observed with the combination in both chemotherapy-naive and pretreated patients with colorectal cancer.

The major adverse effects associated with CPT-11 are neutropenia and delayed diarrhoea [37]. However, with increasing experience and awareness of the safety profile of CPT-11 and the development of measures to control adverse events (e.g. the use of antidiarrhoeals such as loperamide and Tiorfan®, and broad spectrum antibiotics in cases of persisting diarrhoea), the tolerability of CPT-11 has improved during the course of the clinical trial programme. Thus, comparing two sequential European phase II studies, incidence of severe (grade 4) delayed diarrhoea and febrile neutropenia (± infection) were reduced from 8 to 2.5% and from 12 to 6%, respectively.

CONCLUSION

Colorectal cancer is a commonly-occurring malignancy for which there is currently only one anticancer agent which has established efficacy. During the 40 years since the introduction into clinical practice of 5-FU, the only improvements on the modest response rates achieved with this agent have been through the use of administration techniques and/or concomitant agents that modulate 5-FU activity. In this respect, the combination of 5-FU and folinic acid has been the most successful. Nevertheless, there remains considerable scope for improving the outcome in patients with colorectal cancer. In particular, in patients who have failed to respond or have relapsed following 5-FU-based chemotherapy, there are currently no second-line therapies with established efficacy. CPT-11 is a novel anticancer agent which acts on DNA-topoisomerase I, an enzyme which is highly expressed in colorectal cancer cells, and represents a significant advance in the management of this disease. The activity of CPT-11 has been demonstrated in human tumour cell lines including those expressing the MDR phenotype. These results have been supported by encouraging response rates in clinical trials in both chemotherapy-naive and pretreated patients with advanced colorectal cancer and also in other tumours generally considered to be resistant to anticancer agents. Indeed, the level of clinical activity observed with CPT-11 monotherapy, whether given at a dosage of 350 mg/m^2 every 3 weeks or 100–150 mg/m^2 every 1–2 weeks, appears to be at least equivalent to that of 5-FU/folinic acid. Further studies are ongoing to define the optimum

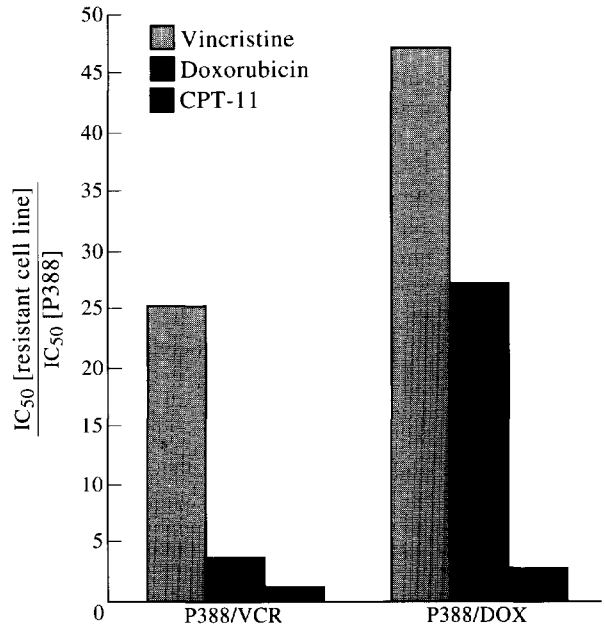


Figure 2. Comparison of resistance to vincristine, doxorubicin or CPT-11 in cell lines that are resistant to vincristine (P388/VCR) and doxorubicin (P388/DOX), calculated as relative activity (IC_{50}) of each drug in resistant versus non-resistant (P388) cell lines [20].

dosage schedule for CPT-11, to further improve the safety profile of the drug and also to fully assess the utility of CPT-11 in combination with 5-FU and other chemotherapeutic agents.

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