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CPT-11 (Irinotecan) in the Treatment of Colorectal Cancer

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Colorectal cancer is one of the most common cancers in the Western World. Although 50% of patients are cured by surgery alone, the outcome is poor in high-risk patients (Dukes stages B2 and C) despite adjuvant chemotherapy with 5-fluorouracil (5-FU)-based regimens. CPT-11 (irinotecan) is a promising new agent for the treatment of colorectal cancer with a unique mechanism of action. CPT-11 is a DNA topoisomerase I inhibitor, which has not demonstrated susceptibility to the P-glycoprotein-mediated multidrug-resistant phenotype. Phase II studies with CPT-11 have demonstrated definite activity against colorectal cancer in both chemotherapy-naive and pretreated patients (response rates of 15–32% observed) even with clinical evidence of resistance to 5-FU. The response rate appears to be consistent, reproducible and equivalent to that achieved with 5-FU plus folinic acid in chemotherapy-naive patients.

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INTRODUCTION

COLORECTAL CANCER is one of the most common cancers in the Western World and is second only to lung cancer as a cause of cancer death in the U.S.A. The incidence of the disease in the U.S.A. and Europe is currently estimated at 300 000 cases per annum [1].

CURRENT TREATMENT OPTIONS

Surgery is currently the first-line treatment for resectable colorectal cancer, although approximately 50% of patients who have undergone surgery will eventually die of metastatic disease [1]. Current therapeutic strategies in this setting centre on 5-fluorouracil (5-FU). Indeed, over 30 years after its introduction into clinical practice, this agent remains the most effective drug available for the treatment of colorectal cancer despite the low response rates it achieves. For example, in the treatment of patients with advanced, metastatic colorectal cancer, response rates to 5-FU alone are usually less than 20% [2]. Newer strategies have focused on enhancing the therapeutic efficacy of 5-FU while avoiding the systemic administration of higher doses of the drug. One such approach is the combination of 5-FU with folinic acid.

A meta-analysis of nine studies involving over 1300 patients with advanced colorectal cancer showed an improvement in overall tumour response rate with 5-FU plus folinic acid when compared to 5-FU alone (23 versus 11%), although an overall improvement in survival was not demonstrated [2]. However, another meta-analysis demonstrated an improvement in overall tumour response rate and survival with 5-FU plus methotrexate when compared with 5-FU alone [3]. Furthermore, two recent randomised trials demonstrated prolonged survival when patients were treated with 5-FU-based regimens in comparison with supportive care alone [4, 5].

Other agents have been used in combination with 5-FU in the treatment of advanced colorectal cancer with only limited success. Although an objective response rate of between 26 and 42% has been demonstrated with a combination of 5-FU and interferon, this regimen has been associated with significant toxicity principally comprising gastrointestinal and haematological effects, mucositis and neurotoxicity [6–8].

The poor response rate associated with 5-FU in the treatment of advanced colorectal cancer highlights the urgent need for more effective chemotherapeutic options. This is particularly imperative for patients who fail on 5-FU therapy and for whom there is currently no second-line treatment option; a regimen of 5-FU with folinic acid will generally produce a response rate of 10% or less in patients previously treated with 5-FU [9]. Of the new agents currently under investigation, the topoisomerase I inhibitor, CPT-11 (irinotecan), appears particularly promising.

CPT-11

CPT-11 is a semi-synthetic, soluble derivative of the plant alkaloid camptothecin. During the early 1970s, camptothecin demonstrated significant activity against several experimental tumour models but was associated with severe toxicity [10, 11]. Clinical development was subsequently halted and attempts were made to synthesise less toxic derivatives. These investigations led to the identification of several highly active analogues including CPT-11 and topotecan. CPT-11 is metabolised by the liver to its active metabolite 7-ethyl-10-hydroxy-camptothecin (SN-38) [12]. CPT-11 retains the lactone ring characteristic of camptothecin but has an additional piperido side-chain at position 10 which improves the solubility of the compound. Topotecan, by

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comparison, incorporates a stable basic side-chain at position 9 [12].

Mechanism of action

Camptothocin and its analogues possess a unique mechanism of action whereby they target the eukaryotic DNA enzyme topoisomerase I [13, 14]. DNA topoisomerases are nuclear enzymes responsible for controlling the topology of the supercoiled DNA double helix during the replication and translation of genetic material. Two major types of topoisomerase enzymes have been identified, topoisomerase I and II [15]. Topoisomerase I enzymes produce transient single-stranded DNA breaks independent of ATP, while topoisomerase II enzymes are responsible for transient double-stranded DNA breaks and require ATP to function [16]. During S-phase, progression of the replication fork requires one end of the DNA double helix to separate; this is facilitated by the topoisomerase enzymes unwinding the DNA double helix ahead of the replication fork. During this process a covalent linkage is formed between the topoisomerase and DNA, termed a cleavable complex. Topoisomerase-active anticancer drugs stimulate and stabilise this complex. It is thought that camptothecin and its analogues cause the collision of cleavable complexes with moving replication forks. This leads to the arrest of DNA replication and irreversible DNA strand breaks and ultimately, results in cell death [12, 15].

Topoisomerase I levels are greatly elevated in some cancer tissues compared with levels in normal mucosa. For example, in colon cancer cells, levels up to 14–16 times higher than those in normal tissue have been measured [17]. Topoisomerase I is also present in relatively high concentrations in both proliferating and quiescent cells, suggesting that topoisomerase I inhibitors affect slowly as well as rapidly proliferating tumours [18]. In addition, camptothecin and CPT-11 have not been shown to be subject to the P-glycoprotein-mediated multidrug-resistant phenotype [19, 20].

Clinical efficacy

In preclinical studies CPT-11 demonstrated antitumour activity against human tumour cell lines resistant to vincristine, doxorubicin, colchicine and vinblastine [19]. Antitumour activity has also been demonstrated against colorectal, ovarian, non-small cell lung, breast and mesothelioma human tumour colony-forming units [21]. Subsequent phase I and II clinical studies of CPT-11 have produced promising results in the treatment of patients with colorectal cancer. These are reviewed below. Interestingly, despite a common mechanism of action, CPT-11 but not topotocan [22] has demonstrated important cytotoxic activity against advanced colorectal cancer in clinical studies.

Phase I studies

Three intravenous dosage schedules of CPT-11 were investigated in 235 patients enrolled in European phase I studies (Table 1) [23–25]. These included one dose every 3 weeks; weekly dosing for 3 of every 4 weeks; or daily dosing for 3 consecutive days every 3 weeks. The maximum tolerated dosage (MTD) of CPT-11 was defined as the dose level at which more than 50% of patients experienced grade 3 or 4 of the same type of toxicity (with the exception of emesis and alopecia). Independently of the European studies, phase I studies were conducted in Japan [26–28] and the U.S.A. [29, 30] using varying dosage schedules of CPT-11. These studies produced divergent results compared to the European studies partly because of differences in the definition of MTD and because gastrointestinal toxicity could be circumvented in the once every 3 weeks European study [24].

Early in the European phase I studies, responses were noted in patients with colonic and oesophageal cancers, head and neck cancer, cervical and breast cancers, pancreatic cancer and hepatocarcinoma. Abigerges and colleagues [24] reported six partial responses in patients with colon cancer refractory to 5-FU. The improved response rate observed with different dosages of CPT-11 (450–750 mg/m^2) administered once every 3 weeks suggests that the activity of CPT-11 is dose-dependent [24].

CPT-11 was found to have a terminal half-life of 9.3–14.2 h [23, 24, 31] which is considerably longer than that cited for topotecan (3 h) [12]. This could be a potential advantage clinically, in that tumour cells will be exposed *in vivo* to CPT-11 and its metabolite, SN-38, for a relatively long period of time, making the frequent administration of CPT-11 unnecessary.

In the European studies, the dose-limiting toxicity of CPT-11 for all three dosage schedules investigated was neutropenia and delayed diarrhoea. The neutropenia associated with the administration of CPT-11 was found to be schedule-dependent and dose-related but not cumulative. Neutrophil nadir was reached on days 21–25 with the weekly schedule [23] and on days 6–9 with the once every 3 weeks schedule [24], with a median time to recovery of 5 days. Delayed diarrhoea was also schedule-dependent and dose-related but not cumulative, and the median time to onset was 6 days after the administration of CPT-11 [24]. The use of high-dose loperamide was shown to counteract the diarrhoea, enabling a higher dosage of CPT-11 to be administered [24, 32]. In the future, the new encephalinase inhibitor Tiorfan may also circumvent the problem of diarrhoea [33]. Other toxicities experienced with CPT-11 in phase I studies included emesis, anaemia, asthenia, alopecia, abdominal pain, and more rarely, reversible elevation of hepatic transaminases and skin toxicity.

The MTDs for the various dosage regimens were 145 mg/m^2 with the weekly schedule, 115 mg/m^2 with the 3 consecutive days schedule and 600 mg/m^2 with the once every 3 weeks schedule. With the latter schedule, high-dose loperamide was administered to control the diarrhoea and to allow for dose escalation above the 250 mg/m^2 dosage schedule recommended by the American and Japanese phase I studies [24].

From the results of the European phase I studies, CPT-11 at a dosage of 350 mg/m^2 administered once every 3 weeks (as a 30-min infusion) was considered to be a rational choice for phase II studies compared to the other proposed schedules, since it was associated with the highest dose intensity and tolerability. The incidences of diarrhoea and neutropenia were reduced when a patient was switched from an alternative schedule to the 3-weekly schedule. In addition, the planned dose intensity (and actual dose intensity) of the 3-weekly schedule was superior to the planned dose intensity of the weekly schedule in the French study [23]. This schedule was also considered to be the most convenient for treatment in an out-patient setting.

Phase II studies

In view of the activity noted with CPT-11 in phase I studies in patients with colorectal cancer, phase II studies in this tumour type were performed. The clinical efficacy of intravenous CPT-11 in the treatment of colorectal cancer has now been investigated in phase II studies conducted in Japan, Europe and the U.S.A. (Table 2). CPT-11 appears promising as both a first-line agent administered to chemotherapy-naive patients and as a second-

Table 1. Results of phase I studies with CPT-11 in patients with various tumour types

Reference	Dosage schedule	Number of patients	Number of courses	Maximum tolerated dosage (MTD)
European studies				
Catimel *et al.* [25]	33–115 mg/m² for 3 consecutive days every 3 weeks (30-min infusion)	46	150	115 mg/m²/day
Abigerges *et al.* [24]	100–750 mg/m² every 3 weeks (30-min infusion)	64	190	600 mg/m² every 3 weeks with high-dose loperamide
De Forni *et al.* [23]	50–145 mg/m² weekly for 3 of 4 weeks (30–90-min infusion)	59	304	145 mg/m²/week
Japanese studies				
Ohe *et al.* [28]	5–40 mg/m² daily for 5 days (continuous infusion)	36	–	30 mg/m²/day
Negoro *et al.* [27]	50–150 mg/m² weekly (90-min infusion)	17	74	100 mg/m²/week
Taguchi *et al.* [26]	50–350 mg/m² every 4 weeks	21	–	250 mg/m² every 4 weeks
U.S. studies				
Rowinsky *et al.* [30]	100–345 mg/m² once every 3 weeks (90-min infusion)	32	144	240 mg/m² every 3 weeks
Rothenberg *et al.* [29]	40–180 mg/m² every week for 4 weeks followed by a 2-week rest (90-min infusion)	32	118+	150 mg/m²/week

Table 2. Results of phase II studies with CPT-11 in patients with colorectal cancer

Reference	Dosage schedule	Prior chemotherapy	Number of patients			Response rate [95% CI]
			Evaluable	CR	PR	
Conti *et al.* [34]	125 mg/m² weekly for 4 of 6 weeks	None	19	—	6 (plus 3 minor responses)	32% [NA]
Pitot *et al.* [36]	125 mg/m² weekly for 4 of 6 weeks	None	13	?	?	15% [NA]
Bugat *et al.* [35]	350 mg/m² every 3 weeks	None	48*	?	?	18% [3.9%; 32.6%]
Bugat *et al.* [35]	350 mg/m² every 3 weeks	All patients (5-FU-based regimen)	130*	?	?	17.7% [11.5%; 25.5%]
Pitot *et al.* [36]	125 mg/m² weekly for 4 of 6 weeks	All patients (regimen unknown)	21	—	5 (unknown whether CR or PR)	24% [NA]
Rothenberg *et al.* [38]	125 or 150 mg/m² weekly for 4 of 6 weeks	All patients received 5-FU	44	1	10	25% [12%; 38%]
Shimada *et al.* [37]	100 or 150 mg/m² every 2 weeks	81% of patients received fluoropyrimidines, 5-FU or 5-FU plus folinic acid	63	—	17	27% [16%; 38%]. In patients who previously received 5-FU, RR = 22% [NA]

CR, complete response; PR, partial response; RR, response rate; NA, not available.
*Eligible patients.

line agent in patients pretreated with a cytotoxic agent, e.g. 5-FU.

A number of different CPT-11 treatment schedules have been evaluated in chemotherapy-naive patients. Conti and colleagues [34] administered CPT-11 (125 mg/m²) as a weekly infusion for 4 of every 6 weeks. Among the 19 evaluable patients, six partial responses (32%) and three minor responses were achieved. In a study conducted by Bugat and colleagues [35], a response rate of 18.8% (95% confidence interval 8.9–32.6%) was observed in 48 eligible, chemotherapy-naive patients. In a further study conducted by Pitot and colleagues [36], preliminary results with CPT-11 at a dosage of 125 mg/m² administered weekly for 4 of every 6 weeks indicate a response rate of 15% in 13 evaluable patients.

Although different schedules and dosage regimens have been used in studies evaluating the efficacy of CPT-11 as a second-line agent for the treatment of colorectal cancer, similar response rates of 17.7–27% have been achieved [35–38]. These results are particularly notable in view of the poor prognosis for patients who have relapsed following prior chemotherapy.

Bugat and colleagues [35] assessed the efficacy of CPT-11 (350 mg/m² intravenously once every 3 weeks) in patients with metastatic colorectal cancer who had been previously treated with 5-FU-based chemotherapy. A response rate of 17.7% (95%

confidence interval 11.5–25.5%) was observed in 130 eligible patients. More important than the response rate were the median time to achieve an objective response and the median duration of objective response which were 9.3 weeks and 9.1 months (range 1.6–17 months), respectively.

Other studies to assess the efficacy of CPT-11 as a second-line agent have been conducted in Japan and the U.S.A. Shimada and colleagues [37] evaluated 63 patients with metastatic colorectal cancer (WHO performance status of 0 or 1 in 46 patients) and with metastatic sites in the liver (63%) and lung (44%). Despite 81% of the patients having received prior chemotherapy, an overall response rate of 27% (95% confidence interval 16–38%) was achieved with a CPT-11 dose of 100 or 150 mg/m^2 administered every 2 weeks. In patients who had previously received 5-FU therapy, a response rate of 22% was achieved. The median overall duration of response was 208 days (6.9 months) [range 99–381 days; 3.3–12.7 months].

Two U.S.A. studies using a weekly dose of 125 or 150 mg/m^2 CPT-11 (for 4 of every 6 weeks) have achieved similar results. 44 patients were evaluated for response in a study conducted by Rothenberg and colleagues [38]. One complete and 10 partial responses were observed for an overall response rate of 25% (95% confidence interval 12–38%) in the evaluable population (n = 44). In this study, the responding patients could be identified early, as 10 of the 11 objective responses occurred by the end of the second treatment cycle. The North Central Cancer Treatment Group (NCTG) is currently conducting a study using CPT-11 at a weekly dose of 125 mg/m^2 (for 4 of every 6 weeks) in patients with metastatic colorectal cancer. Although the results are only preliminary, an objective tumour response has been observed in 5 of 21 previously treated patients (response rate 24%) [36].

Adverse effects

The adverse effects reported with CPT-11 in these phase II studies were similar to those noted in phase I trials. The most common adverse effects were diarrhoea and neutropenia.

Severe diarrhoea (grade 3 or 4) developed in 13–47% of patients who received CPT-11 at a dosage of 125 or 150 mg/m^2 weekly for 4 of 6 weeks [34, 36, 38] or every 2 weeks [37]. However, the administration of loperamide reduced the incidence of grade 4 diarrhoea from 15 to 5% in one study [38] and in a further study the administration of both loperamide and diphenoxylate reduced the incidence of grade 3 or 4 diarrhoea by 29% to 13% of patients [34].

Grade 3 or 4 neutropenia developed in 16–20% of patients [34, 36–38]. Other adverse effects included alopecia, nausea and vomiting and reversible hepatotoxicity. Assessment of the safety of CPT-11 at a dosage of 350 mg/m^2 every 3 weeks in 213 patients in the European phase II studies resulted in a similar profile of adverse effects [39]. Grade 3 or 4 neutropenia developed in 47% of patients with a median duration to nadir of 8 days and total recovery by day 21 ± 3 in 97% of cycles. Febrile neutropenia developed in 33 patients and life-threatening septicaemia was observed in 9 patients. Grade 3 or 4 delayed diarrhoea occurred in 39% of patients (12% of cycles) and 6% of the episodes were considered to be severe. 81% of patients developed alopecia. In this study, 12% of patients required a dose reduction and treatment delay was necessary in 22%. Of the deaths which occurred in this multicentre study, four were considered to be probably related to CPT-11; one due to septic shock, one due to diarrhoea and two from septic shock and diarrhoea. From our personal experience, most of the deaths were reported in the early phase of the trial and associated with an underestimation of the extent of the gastrointestinal toxicity and inadequate treatment.

CONCLUSION

In phase I and phase II studies, CPT-11 has demonstrated definite activity in the treatment of chemotherapy-naive and pretreated patients with colorectal cancer. This activity is maintained even in patients who have progressed while on a 5-FU regimen as first-line treatment. Although the response rate of 15–32% achieved with CPT-11 may be considered low in other therapeutic areas, it is still higher than the response rate observed with 5-FU alone and comparable to that of the combination of 5-FU with folinic acid [2, 40]. The response rate with CPT-11 also appears to be consistent and reproducible.

Additional studies are required to further demonstrate the benefit–risk ratio of CPT-11 at the current recommended dosage schedule in patients with colorectal cancer. Second-line confirmatory phase II studies and a phase III study to assess quality of life and survival are planned or are already ongoing. In an effort to control CPT-11-induced diarrhoea more effectively, two further randomised studies are currently investigating the optimal symptomatic treatment of delayed diarrhoea and the role of the encephalinase inhibitor Tiorfan in this setting.

Phase II studies have confirmed the efficacy of the 3-weekly schedule of CPT-11 at a dose of 350 mg/m^2. However, other dosage schedules used in Japanese and American studies have also produced promising results suggesting the need for further studies to confirm the optimum dosage and schedule for CPT-11.

In addition to using CPT-11 as a single agent, the drug may also have potential when used in combination with 5-FU plus folinic acid for first-line treatment of colorectal cancer. This may be possible because CPT-11 and 5-FU have entirely different mechanisms of action. Moreover, CPT-11 is unlikely to share the same mechanism of drug resistance as 5-FU given that it has demonstrated activity in patients who were progressing on 5-FU therapy. Also of interest are the results from a recent phase I study demonstrating a potential pharmacokinetic interaction between CPT-11 and 5-FU in patients with metastatic colorectal cancer [41].

In conclusion, CPT-11 is an interesting new agent for the treatment of colorectal cancer and further clinical studies are required to fully evaluate its role in this setting.

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