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Review

CPT-11 in Gastrointestinal Cancer

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Colorectal, gastric and pancreatic cancers are major health problems worldwide. Although surgery is a curative option in 50% of patients with colorectal cancer, it is much less effective in gastric cancer (< 20% of patients) and virtually ineffective in pancreatic cancer. These three cancer types also respond poorly to chemotherapy. CPT-11 (irinotecan), a novel cytotoxic drug, is now available in many countries as a single agent for second-line therapy in metastatic colorectal cancer. The response rate in the pivotal European study of metastatic colorectal cancer patients was 14%, with a median duration of response of 8.5 months. There was also a high rate of disease stabilisation (44%), with a median duration of 4.8 months. Median survival time was 10.4 months. The dose-limiting toxicities (DLT) for CPT-11 are delayed diarrhoea and neutropenia, both of which are schedule dependent and non-cumulative. These encouraging data in second-line therapy support the further study of CPT-11 as first-line therapy for colorectal cancer in combination with other agents. Four Japanese trials of CPT-11 as first- and/or second-line single-agent therapy for advanced gastric cancer report response rates of 18–43%. The median durations for response and survival time in the late phase II trial were 2.3 months and 5.8 months, respectively. These results are in the range of those reported for sequential high-dose methotrexate and 5-fluorouracil (5-FU)/doxorubicin (FAMTX), etoposide/leucovorin/5-FU (ELF) or cisplatin/5-FU therapy in gastric cancer. Data are currently available from five phase II studies of CPT-11 in advanced pancreatic cancer: four Japanese and one European. The response rates ranged from 9 to 19%. The median duration of survival for all treated patients in the European study was 5.2 months. CPT-11 in combination with 5-FU is currently being investigated in Japan, the U.S.A. and Europe in patients with gastrointestinal tumours. CPT-11 is also being evaluated in combination with each of the following agents: oxaliplatin, docetaxel, raltitrexed, etoposide and mitomycin C. Japanese studies of CPT-11 plus cisplatin in patients with gastric cancer have produced response rates of 48–59%. These encouraging data highlight the potential for CPT-11 in combination therapy for gastrointestinal tumours. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

Gastrointestinal cancers

COLORECTAL, GASTRIC and pancreatic cancers are major health problems worldwide. Prognosis of gastric and pancreatic cancers is particularly grim; patients are often reported as having metastatic cancer at the first diagnosis [1, 2]. Surgery is a curative option in 50% of colorectal cancers, but is less effective in gastric cancer, where the overall 5-year survival rate is less than 10%. In pancreatic cancer, surgical cure rates of 0–18% are reported. These three cancer types also respond poorly to current chemotherapy. New approaches to treatment are, therefore, required to improve upon the results currently obtained with the recommended combinations of surgery and chemotherapy.

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For 40 years, 5-fluorouracil (5-FU) and 5-FU-based treatment regimens have been the mainstay of chemotherapy for the treatment of gastrointestinal cancers. Both adjuvant and palliative treatment schedules are applicable in colorectal cancer. However, because of the advanced stage of disease frequently encountered at diagnosis of gastric and pancreatic cancers, palliative chemotherapy is usually the only treatment option in these tumours. Although response rates to 5-FU and combination regimens are often low in patients with gastrointestinal tumours, improvements in survival and quality of life have recently been achieved with new dosage schedules and drug combinations and can, no doubt, be further improved upon. Important recent data indicate that both the response rate and stabilisation rate following chemotherapy are indicative of the survival rate for colorectal cancer patients [3, 4]. Toxicities common with 5-FU and modulators include diarrhoea, vomiting, stomatitis and neutropenia [5, 6].

CPT-11: a novel chemotherapy

This paper will review and discuss the available data on CPT-11 (irinotecan) in gastrointestinal tumour therapy and the validity of further clinical research into CPT-11 therapy for metastatic colorectal, gastric and pancreatic cancers. CPT-11 is a semi-synthetic, water-soluble derivative of the plant alkaloid camptothecin. After conversion to its active metabolite, SN-38, CPT-11 acts by inhibiting the eukaryotic enzyme DNA-topoisomerase I [7, 8]. This unique mechanism of action for CPT-11 is distinct from that of 5-FU, and, therefore, opens up the opportunity for 5-FU and CPT-11 therapeutic combinations without cross-resistance [9]. Phase I data show that CPT-11, folinic acid and 5-FU can be combined with acceptable tolerability. The metabolism of CPT-11 is not altered by the concurrent medication. The recommended single-agent dose of CPT-11 is 350 mg/m^2 given as a 30 min infusion once every 3 weeks. The dose can be reduced to 300 or 250 mg/m^2 if neutropenia develops.

CPT-11: pharmacokinetics. Relatively high plasma concentrations of the SN-38 glucuronide conjugate, SN-38G, suggest that its formation and elimination could play an important role in the therapeutic effect of SN-38. Low levels of SN-38 glucuronide formation, implying hepatic impairment, were found to be associated with gastrointestinal toxicity in one study [10], although this was not confirmed by others [11]. Some studies have reported a significant decrease in the neutrophil count with the area under the concentration-versus-time curve (AUC) of CPT-11 and SN-38 using different CPT-11 administration schedules [11–13]. Furthermore, a relationship between these parameters and delayed diarrhoea has been identified when the sample size is large enough [13].

COLORECTAL CANCER

Colorectal cancer is the second leading cause of cancer deaths in the Western world and accounts for 10–12% of all cancers [14]. There are estimated to be 300 000 new cases of colorectal cancer in the U.S.A. and Europe per year. Colorectal cancer is curable by surgical treatment if diagnosed in the early stages. However, approximately half of all patients who have undergone surgery will develop metastatic disease [14]. For these patients, 5-FU-based regimens remain the first-line chemotherapeutic option. Modulation of 5-FU therapy with low-dose leucovorin (folinic acid)—the 'Mayo Clinic' schedule—is frequently used. Whilst this combination has shown a significant benefit in terms of tumour response rate over single-agent 5-FU (23% versus 11%), no advantage in the median survival time was reported, although these studies were not designed to answer this question. However, chemotherapy does provide a survival advantage, as demonstrated by comparisons made between treatment versus no treatment. Treatment with chemotherapy (sequential methotrexate and 5-FU with leucovorin) before symptoms appear also prolongs the symptom-free period by 8 months and survival by 5 months [15].

Advanced colorectal cancer has long been considered poorly sensitive to chemotherapy. The prognosis for patients with advanced disease who fail to respond to a 5-FU-based therapy is particularly poor, and second-line treatments in patients previously treated with 5-FU-based regimens typically achieve response rates ranging from 0 to 24% [16–19]. New agents are urgently needed for use in either first- or second-line chemotherapy.

CPT-11 in colorectal cancer

CPT-11 is now available in many countries as a single agent for second-line therapy in metastatic colorectal cancer. Several phase I and II studies have been completed in Europe, Japan and the U.S.A.; these phase I and II studies have been extensively reviewed [20–22]. Of particular interest are the collective results from four European phase II studies involving 455 colorectal cancer patients with documented resistance to 5-FU [23].

CPT-11 administered at a dosage of 350 mg/m^2 as a 30–90 min intravenous infusion once every 3 weeks produced an overall response rate of 13% (10–17%) in 363 eligible patients. The median duration of response and time to disease progression were 7.6 months and 4.1 months, respectively. There was also a high rate of disease stabilisation (42%), which lasted for a median duration of 5.1 months. The median survival time was 9.5 months, with 14.5 months and 12.5 months reported for responders and patients with stable disease, respectively. Control of tumour growth was associated with improvement or stabilisation of weight and performance status in many patients who had disease progression on study entry. Relief of pain, with reduced analgesic consumption was reported in 61% of responding or stabilised patients, compared with 34% in patients with progressive disease ($P = 0.003$). Furthermore, 4 months after commencing treatment, 74% of patients with tumour growth stabilisation were free of pain and had performance status values of 0 or 1 (all patients had a performance status value of 0–2 before starting the treatment). All these factors have been associated with an improved quality of life [23].

Similar efficacy results have been observed in U.S. multicentre studies involving 304 patients administered CPT-11 once a week for 4 weeks, followed by 2 weeks' rest. The preferred CPT-11 dose was reported to be 125 mg/m^2 [24]. The response rate was 15% (10–20%) with a median duration of 6 months and a median survival time of 9 months. A further 49% of patients had disease stabilisation and the overall median time to progression was 4 months [24].

Two phase III trials of CPT-11 in second-line therapy for metastatic colorectal cancer are now completed and awaiting publication: CPT-11 versus best supportive care [25] and CPT-11 versus 'best' estimated 5-FU infusional regimen chosen by each clinic from three regimens [26]. Both studies showed CPT-11 to be effective in the treatment of metastatic

colorectal cancer in terms of survival, clinical benefit and quality of life. Both recommended the use of CPT-11 after 5-FU failure.

CPT-11: safety profile

The dose-limiting toxicities (DLT) reported for CPT-11 are delayed diarrhoea and neutropenia [12, 27–29]. These adverse events are both schedule-dependent and non-cumulative. Early treatment of delayed diarrhoea with high-dose loperamide [9] or acetorphan plus loperamide [30] is reported to reduce the frequency of grade 3/4 delayed diarrhoea from 39% [31] to 27% [9]. The incidences of neutropenia and diarrhoea reported by Van Cutsem and colleagues [9] are comparable with those published for 5-FU/leucovorin in the Mayo Clinic schedule [5]. A significant improvement in the understanding of the cause and management of delayed diarrhoea associated with CPT-11 therapy has improved its toxicity profile [13]. A recent study indicates measurement of baseline bilirubin levels as a possible predictor of severe neutropenia and diarrhoea associated with CPT-11 therapy [32]. Further improvements in the prevention of adverse reactions are expected as studies are designed to modify the dose on an individual patient basis.

New applications for CPT-11

When given as a single agent in first-line treatment, partial responses of 19–32% and minor responses of 12% were seen, confirming that CPT-11 is active in first-line therapy [33, 34]. These results, together with the knowledge that CPT-11 and 5-FU have markedly different mechanisms, raise the possibility of using CPT-11 in combination in first-line chemotherapy (see section on CPT-11 in combination therapy for colorectal cancer). Furthermore, data from recent phase I and II trials indicate the therapeutic potential of CPT-11 for gastric [35, 36] and pancreatic [37] cancers.

GASTRIC CANCER

The incidence of gastric cancer, whilst decreasing throughout the Western world, is increasing in Japan. In the U.S.A., the incidence is now 9 cases per 100 000, compared with 100 per 100 000 in Japan, where gastric cancer is the number one cause of death [38, 39]. In Western countries, adenocarcinomas of the oesophagogastric junction are steadily increasing and could exceed in incidence gastric adenocarcinomas of other localisations. Survival of patients with gastric cancer is poor, with an overall 5-year survival rate of less than 10% [40], and gastric cancer should be viewed as disseminated even at the early stages of disease [1].

A recent analysis of randomised clinical trials of adjuvant chemotherapy in resectable gastric cancer highlighted limitations in many of the studies: wide variability in the prognostic factors, inadequate staging within the treatment groups and inadequate details of surgical techniques [41]. Only six of the 24 analysed trials demonstrated a significant prolongation of survival with the treatment investigated. Major biases were identified and no adjuvant treatment could be recommended as standard therapy.

Second-generation treatment regimens under development for advanced gastric cancer include the following combinations: sequential high-dose methotrexate and 5-FU/doxorubicin (FAMTX), etoposide/doxorubicin/cisplatin (EAP), etoposide/leucovorin/5-FU (ELF) and variants of these regimens [42–44]. In an ongoing phase III study comparing FAMTX, ELF and cisplatin/5-FU in patients with advanced gastric cancer, a realistic response rate of 21–27% can be expected with a median survival of approximately 6.9 months [45]. No significant differences in response or survival have been found to date between the three treatment regimens. However, chemotherapy has been seen to provide a significant benefit in the quantity and quality of life over best supportive care alone. 5-FU, leucovorin and etoposide (minus etoposide in elderly patients with a poor performance status) plus best supportive care was also compared with a best supportive care regimen where chemotherapy was allowed only where supportive care alone did not provide sufficient palliation. The chemotherapy regimen was associated with a trend to longer median survival (8 versus 5 months), increased median time to subjective disease progression (6 versus 2 months), increased quality adjusted survival (6 versus 2 months) and improved quality of life: 45% of patients versus 20% of patients allocated to best supportive care only [46]. Whilst no one combination treatment regimen is recognised as standard for gastric cancer, continuous infusion 5-FU combined with cisplatin is currently considered to be a suitable reference treatment worldwide.

Several agents have recently emerged as potential new options for advanced gastric cancer. Promising data have been generated with CPT-11 [33], docetaxel [47–49] and cisplatin [50], each administered as single agents. A logical way forward now in gastric cancer therapy would be to combine CPT-11 and docetaxel with a 5-FU-based regimen. In a recent paper [51], a combination of epirubicin, cisplatin administered once every 3 weeks and 5-FU administered as a protracted venous infusion, provided significant benefits over FAMTX in first-line chemotherapy. Response rates were 45 versus 21%, survival 8.9 versus 5.7 months and 1-year survival 36 versus 21% for epirubicin, cisplatin and 5-FU versus FAMTX. The cisplatin-containing regimen also improved quality of life scores at 5.6 months. The authors concluded that this should be the standard treatment for advanced oesophagogastric cancer.

CPT-11 therapy in gastric cancer

CPT-11 has been administered to patients with advanced gastric cancer, both as a single agent (Table 1) and in combination with 5-FU or cisplatin. The use of CPT-11 in combination therapies for gastric cancer is presented below.

CPT-11: single-agent therapy in advanced gastric cancer. To date, all trials of CPT-11 in advanced gastric cancer have been conducted in Japan. Three early phase II trials [36, 52, 53] found that CPT-11 produced response rates of 25–43% (Table 1). In the first two studies, patients had failed on previous chemotherapy. Leucopenia, nausea/vomiting, alopecia, anorexia, anaemia and diarrhoea were the most common toxic events. Different schedules and starting doses were investigated: CPT-11 100 mg/m^2 intravenously, once a week; 150 mg/m^2 intravenously once every 2 weeks; and 200 mg/m^2 intravenously every 3–4 weeks.

A late phase II study of CPT-11 in relapsed or advanced gastric cancer patients compared two intravenous dosage schedules: 100 mg/m^2 once a week, and 150 mg/m^2 once every 2 weeks [35]. The overall response rate for the 76 eligible patients was 18%. Of the 56 patients previously treated with chemotherapy, 16% responded compared with 25% of

Table 1. *CPT-11 single-agent therapy in advanced gastric cancer patients: summary of efficacy data*

CPT-11 dosage schedule(s)	Trial phase	No. of gastric cancer patients analysed/no. treated	Response rate (PR + CR) (%)	[Ref.]
100 mg/m^2 infused i.v. once a week 150 mg/m^2 i.v. once every 2 weeks 200 mg/m^2 i.v. once every 3–4 weeks	Early II	NA/19	30.8	[52]
100 mg/m^2 infused i.v. once a week 150 mg/m^2 i.v. once every 2 weeks 200 mg/m^2 i.v. once every 3–4 weeks 50 mg/m^2 for 3 consecutive days every 2 weeks	Early II	16/21	25	[53]
200 mg/m^2 i.v. once every 3 weeks 150 mg/m^2 i.v. once every 2 weeks 100 mg/m^2 infused i.v. once a week	II	7/7	43	[36]
100 mg/m^2 i.v. once a week 150 mg/m^2 i.v. once every 2 weeks	Late II	77/81	18.4	[35]

NA, not available; PR, partial response; CR, complete response; i.v., intravenously.

the 20 chemotherapy-naïve patients. Metastatic lesions in the lymph nodes, lungs and liver responded in 36%, 33% and 17% of cases, respectively. The median dose administered before patients achieved a partial response was 320 mg/m^2. The median survival time was 5.8 months. The incidences of grade 3/4 toxicities observed in the 76 eligible patients were leucopenia (42%), nausea and/or vomiting (12%), alopecia (16%), anorexia (20%), diarrhoea (22%), anaemia (29%) and thrombocytopenia (7%). No significant differences were observed in the frequency or degree of toxicities between the two dosage schedules. Slight, mainly reversible, abnormalities in liver and kidney function were also reported for some patients. The side-effects reported in the four studies were comparable, both in severity and frequency. Further studies could be required to identify the most active schedule.

Combination chemotherapy. The early Japanese phase I study of CPT-11 plus 5-FU in gastrointestinal tumour patients, as reported in the colorectal cancer section, included patients with gastric cancer. The smaller AUC for SN-38 in this study indicated that 5-FU or its metabolites might interfere with CPT-11 [54], although these results have not been repeated using a different schedule [55].

The combination of CPT-11 and cisplatin was investigated in a Japanese phase I study of gastric cancer patients. 24 patients were each given a fixed dose of cisplatin 80 mg/m^2 on day 1 combined with CPT-11 60, 70 or 80 mg/m^2 on days 1 and 15, repeated every 4–6 weeks. The overall response rate was 42% (10/24) and the median duration of response was 4.6 months. The maximum tolerated dose (MTD) was CPT-11 80 mg/m^2 with cisplatin 80 mg/m^2, and the DLT was neutropenia. However, Shimada and colleagues recommended that CPT-11 70 mg/m^2 and cisplatin 80 mg/m^2 be used for phase II studies. The phase II study using this schedule included 44 patients with advanced gastric cancer, of whom 29 were chemotherapy-naïve [56]. The response rate in the chemotherapy-naïve patients was 59% and included 1 complete response. In patients who had received previous chemotherapy, the response rate was 27%, and the overall response rate was 48%. The median duration of response was 3.9 months. The response rate was also measured by target organ: primary (21%), liver (40%), lymph node (37%), lung (50%) and others (25%). The DLT was neutropenia which was reported as grade 4 for 36% of patients. All toxicities were reversible and there were no treatment-related deaths. The overall median survival was 10.2 months. This treatment regimen will be further evaluated in a phase III study to determine survival benefit.

PANCREATIC CANCER

The incidence of pancreatic cancer is increasing worldwide, with a current average annual incidence in the U.S.A., Canada, northern Europe and Japan of 8 per 100 000 [57]. The prognosis of patients with advanced pancreatic cancer is extremely poor, with only 0–18% of patients surviving 5 years. Surgical resection is the only curative option. However, most patients have unresectable disease at the time of diagnosis, as pancreatic cancers remain undetected until local invasion and/or distant metastases develop [2].

No effective chemotherapy has yet been established for advanced pancreatic cancer [58, 59]. Over the past 10 years, the most frequently used single chemotherapeutic agents have been 5-FU, cisplatin, epirubicin and ifosfamide [2]. The administration of 5-FU in the various dosage schedules used for colorectal cancer has produced response rates of < 10%, with median survival rates not exceeding 6 months [60–62]. Nevertheless, two recent trials which compared 5-FU-based regimens with best supportive care have shown a significant increase in median survival (6 versus 2.5 months) and an increase in the quality of life of patients following chemotherapy compared with best supportive care alone [63, 64]. No clinically significant activity was reported for the other chemotherapeutic agents [65–67].

Several new therapeutic agents are now emerging for advanced pancreatic cancer. Gemcitabine has recently been proposed as a standard treatment for advanced pancreatic cancer in the U.S.A. based on symptomatic relief and a small but statistically significant improvement in median survival (5.7 versus. 4.4 months with 5-FU; $P = 0.0025$) [68]. In addition, Rougier and colleagues [69] reported encouraging results from a trial of docetaxel in patients with pancreatic cancer. Furthermore, a response rate of 32% was reported with 5-FU plus cisplatin in untreated metastatic pancreatic cancer patients, with a median survival time of 7 months [70].

CPT-11 therapy in pancreatic cancer

CPT-11: single-agent therapy in pancreatic cancer. Data on CPT-11 in advanced pancreatic cancer are available from five phase II studies: four from Japan and one from Europe (Table 2). Response rates of 13–19% were seen in early phase II studies conducted in Japan. In a late phase II Japanese study of patients with advanced pancreatic cancer, two CPT-11 dosages were tested: 100 mg/m^2 every week and 150 mg/m^2 every 2 weeks. Only 35 of the 57 patients were evaluable for efficacy, with a response rate of 11.4% [37, 71]. The incidences of toxicity (grade 2 or higher) reported in the 57 eligible patients were: leucopenia (61%), anaemia (56%), anorexia (70%), nausea/vomiting (56%), alopecia (40%) and diarrhoea (37%).

In the only European phase II study reported to date, 34 chemotherapy-naïve patients with advanced pancreatic cancer were treated with CPT-11 350 mg/m^2 intravenously once every 3 weeks [58]. 3 of 32 eligible patients (9%) achieved partial responses lasting 7.2–7.8 months. The median duration of survival for all treated patients was 5.2 months. The main grade 3 or 4 toxicities were: leucopenia (50% of patients), diarrhoea (21%), asthenia (32%), nausea (29%) and vomiting (21%). All these toxicities were manageable and reversible. Although the conclusion of the authors was that CPT-11 is not active in pancreatic cancer, this agent deserves further investigation, both as a single agent and in combination.

COMBINATION THERAPIES FOR FIRST-LINE TREATMENT OF GASTROINTESTINAL TUMOURS—THE WAY FORWARD

Pharmacokinetic results from the early Japanese study indicated a negative interaction between CPT-11/SN-38 and 5-FU [54]. In order to clarify a possible interaction, several administration schedules of CPT-11/5-FU combinations are currently being investigated in phase I trials in Japan, the U.S.A. and Europe (Table 3); some of these have been reviewed by Saltz and colleagues [72]. In an early Japanese study of 36 patients with metastatic colorectal cancer, the MTD of CPT-11 was a single dose of 250 mg/m^2 given in combination with a 7 day continuous infusion of 5-FU 400 mg/m^2/day in 3–4 week cycles [54]. This dose of CPT-11 was the same as the MTD observed for single-agent CPT-11 therapy in Japan. The response rate was 11.1%. In an ongoing phase I study with CPT-11 administered 2 days before a 5 day infusion of 5-FU 600 mg/m^2/day in 20 chemotherapy-naïve metastatic colorectal cancer patients, the MTD had not been reached with a dose level of 150 mg/m^2 every 2 weeks [55, 72]. 5 of the 19 evaluable patients (26%) had a partial response at various dosage levels. Toxicity data available for the CPT-11 125 mg/m^2 group showed grade 3/4 neutropenia and diarrhoea in 17% and 20% of patients, respectively. Pharmacokinetic data indicated that there was no interaction between CPT-11, 5-FU or their metabolites.

In a US phase I study of gastrointestinal (mainly colorectal) cancer patients pretreated with 5-FU, the MTD of CPT-11 was 125 mg/m^2 weekly when combined with weekly bolus injections of 5-FU 500 mg/m^2 and leucovorin 20 mg/m^2 for 4 weeks followed by a 2 week rest [73]. This is similar to the usual CPT-11 single-agent dose used in US phase II trials [72]. The DLT was neutropenia, and grade 3/4 diarrhoea developed in 3 of the 17 patients treated using the recommended dose. An ongoing phase II study involving alternating cycles of CPT-11 100 mg/m^2 weekly for 4 weeks followed by a 2 week rest, and then 5-FU 425 mg/m^2 plus leucovorin 20 mg/m^2, both given daily for 5 consecutive days, every 4 weeks, reported a response rate of 32% in previously untreated patients [74].

A European phase I study administered CPT-11 and 5-FU sequentially to pretreated metastatic colorectal (mainly) cancer patients. In the first cycle, CPT-11 was given on day 1 and 5-FU on days 2–6; in cycle 2, 5-FU was given on days 1–5 and CPT-11 on day 6. Treatment was repeated every 4 weeks. The MTD was 350 mg/m^2 for CPT-11 in combination with 5-FU 375 mg/m^2 [75–77]. No unexpected toxicity was reported. In both the US and European studies, which used a crossover design with each patient serving as their own control, no pharmacokinetic interaction between CPT-11 and 5-FU was apparent, although possible synergy cannot be ruled out. Further European phase I/II studies of CPT-11 and 5-FU/leucovorin in first- and second-line therapy are ongoing [82, 83]. These include schedules alternating CPT-11 and 5-FU/folinic acid, which have led to a response rate of 30% with no cumulative toxicity [84], and high-dose

Table 2. CPT-11 single-agent therapy in advanced pancreatic patients: summary of efficacy data

CPT-11 dosage schedule(s)	Trial phase	No. of pancreatic cancer patients analysed/no. treated	Response rate (PR + CR) (%)	Median survival (months)	[Ref.]
100 mg/m^2 infused i.v. once a week 150 mg/m^2 i.v. once every 2 weeks 200 mg/m^2 i.v. once every 3–4 weeks	Early II	7/11	14.3	NA	[52]
100 mg/m^2 infused i.v. once a week 150 mg/m^2 i.v. once every 2 weeks 200 mg/m^2 i.v. once every 3–4 weeks 50 mg/m^2 for 3 consecutive days every 2 weeks	Early II	8/12	12.5	NA	[53]
100 mg/m^2 infused i.v. once a week 150 mg/m^2 i.v. once every 2 weeks 200 mg/m^2 i.v. once every 3–4 weeks	II	16/17	19	NA	[36]
100 mg/m^2 i.v. every week 150 mg/m^2 i.v. every 2 weeks	Late II	35/57	11.4	NA	[37, 71]
350 mg/m^2 i.v. once every 3 weeks	II	32/34	9	5.2	[58]

NA, not available; PR, partial response; CR, complete response; i.v., intravenously.

Table 3. CPT-11 in combination therapy for advanced gastrointestinal cancer patients: summary of results

CPT-11 dosage schedule	Other agent(s) and dosage schedule(s)	Trial phase	No. of eligible patients	Response rate (% of eligible patients)	Pharmacokinetic interaction?	[Ref.]
50–250 mg/m^2, 3–4 week cycle	5-FU 400 mg/m^2/day, 7 day infusion	I	36 CRC	11.1	Yes (antagonism)	[54, 72]
100–175 mg/m^2 given 2 days before 5-FU, every 2 weeks	5-FU 600 mg/m^2/day, 5 day infusion	I	19 CRC	26.3*	No	[55, 72]
100–150 mg/m^2 weekly for 4 weeks, then 2 week break	5-FU 210–500 mg/m^2 bolus + LV 20 mg/m^2, weekly for 4 weeks, then 2 week break	I	42 GI (38 CRC)	17 (CRC)†	No	[73]
100 mg/m^2 weekly for 4 weeks, then 2 week break	5-FU 425 mg/m^2/LV 20 mg/m^2, 5 day infusion every 4 weeks	II	71 CRC	32	NA	[74]
200–350 mg/m^2 single dose, once every 4 weeks	5-FU 375 mg/m^2 daily for 5 days	I	41 (29 CRC)	NA	No	[75–77]
150–200 mg/m^2, 1 h after oxaliplatin, once every 3 weeks	Oxaliplatin 85–110 mg/m^2	I	16 GI* (11 CRC*)	18.2 (CRC)*	Yes (synergism)	[78, 79] (data on file)
140–300 mg/m^2 after docetaxel, once every 3 weeks	Docetaxel 40–70 mg/m^2	I	31	NA	No*	[80]
175–350 mg/m^2, 1 h before raltitrexed, once every 3 weeks	Raltitrexed 2.6 mg/m^2	I	NA (CRC)	NA	NA	(data on file, Rhone-Poulenc Rorer)
60, 70 or 80 mg/m^2 on days 1 and 15, every 4–6 weeks	Cisplatin 80 mg/m^2, day 1 of schedule	I	24 gastric	41.7	NA	
70 mg/m^2 days 1 and 15, every 4–6 weeks	Cisplatin 80 mg/m^2, day 1 of schedule	II	44 gastric	47.7 (all patients) 58.6 (first-line only)	NA	
175–300 mg/m^2 once every 3 weeks	Cisplatin 60–80 mg/m^2 given after CPT-11	I	39*	NA	No*	[85]

*Preliminary data. †$n = 35$. NA, not available; CRC, colorectal cancer; GI, gastrointestinal; LV, leucovorin; 5-FU, 5-fluorouracil.

leucovorin (500 mg/m^2 weekly) used in combination with 5-FU (1.8–2.6 g/m^2 weekly) after CPT-11 (80 mg/m^2 weekly) which resulted in a preliminary response rate of 62% with no DLT observed [85]. Phase III studies investigating the de Gramont schedule or 24 h high-dose infusional 5-FU with or without CPT-11 should be analysed by the end of 1998. Presently there are no available data.

CPT-11 is also under evaluation in combination with other agents. An ongoing phase I trial is investigating CPT-11 in combination with oxaliplatin in patients with gastrointestinal tumours. CPT-11 is given 1 h after oxaliplatin once every 3 weeks. The response rate in patients with 5-FU refractory colorectal cancer was 18% (2 of 11 patients) (data on file, Rhone-Poulenc Rorer). The DLTs were diarrhoea and febrile neutropenia, and the recommended doses for future study were CPT-11 200 mg/m^2 and oxaliplatin 85 mg/m^2 [78, 79] (data on file, Rhone-Poulenc Rorer).

A phase I clinical study is ongoing to investigate docetaxel followed by CPT-11 in various tumour types; both drugs are given intravenously on the same day, once every 3 weeks [80]. Among 36 patients treated to date, the DLT was febrile neutropenia, and two MTDs were reached: docetaxel 70 mg/m^2 plus CPT-11 250 mg/m^2 and docetaxel 60 mg/m^2 plus CPT-11 300 mg/m^2. The recommended dosage for phase II studies was docetaxel 60 mg/m^2 followed by CPT-11 275 mg/m^2 every 3 weeks. The plasma clearance of both CPT-11 and docetaxel, measured during the first chemotherapy cycle in 19 and 18 patients, respectively, was similar to single-agent data over the dose ranges tested.

An ongoing phase I study involves CPT-11 (175–300 mg/m^2) in combination with cisplatin (60–80 mg/m^2) given to patients with solid tumours on day 1, every 3 weeks [81]. The DLT in the first 39 patients were febrile neutropenia and fatigue at the following doses: CPT-11 300 mg/m^2 and cisplatin 80 mg/m^2. Preliminary pharmacokinetic data indicate no interaction between the two drugs.

CPT-11 has been combined with raltitrexed in phase I trials of colorectal cancer patients (data on file Rhone-Poulenc Rorer). Raltitrexed 2.6 mg/m^2 was administered intravenously 1 h after CPT-11, once every 3 weeks. To date, the highest administered doses without DLT are raltitrexed 2.6 mg/m^2 and CPT-11 350 mg/m^2. The safety data are encouraging and the efficacy data for the higher doses are awaited.

These encouraging data on the application of CPT-11 in combination with other chemotherapeutic agents, in particular with 5-FU/leucovorin and oxaliplatin, warrant further clinical studies.

CONCLUSIONS

CPT-11 is established as a new therapeutic agent for second-line therapy in metastatic colorectal cancer patients. Combinations of CPT-11 with other chemotherapeutic agents such as 5-FU, oxaliplatin and raltitrexed have generated encouraging

data in both first- and second-line treatment for colorectal cancer. Recent clinical data highlight the potential for CPT-11 therapy in other gastrointestinal tumours, notably gastric cancer. Combination therapies with 5-FU, oxaliplatin, cisplatin, docetaxel and raltitrexed have also been investigated and preliminary data suggest promising activity levels. The role of CPT-11 in adjuvant therapy should also be investigated and it is envisaged that adjuvant studies could be launched as early as Spring 1999, although the final design has not been decided.

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