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Efficacy of CPT-11 (Irinotecan) as a Single Agent in Metastatic Colorectal Cancer

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The efficacy of CPT-11 (Campto®, irinotecan) given as a single agent has been assessed in three phase II clinical studies of patients with advanced colorectal cancer conducted in Japan, Europe and the U.S. Among a total of 337 evaluable patients treated with CPT-11 in dosage schedules of 100–150 mg/m^2 weekly or bi-weekly (Japan, $n = 63$; U.S., $n = 118$) or 350 mg/m^2 every 3 weeks (Europe, $n = 156$), overall objective response rates ranged from 17 to 27% and the median duration of response was approximately 7–9 months. Prior treatment with chemotherapy did not preclude a response to CPT-11 as evidenced by response rates of 14 to 22% and response durations of approximately 6–8 months in this cohort. In the European study, comparison of chemotherapy-naive patients with those who had received only one 5-fluorouracil (5-FU)-based regimen revealed similar response rates (22 and 20%) and of note, CPT-11 maintained its activity in pretreated patients who had previously experienced progressive disease. Together, these results suggest a lack of cross-resistance between the two agents. Leucopenia and delayed diarrhoea were the major adverse events observed in these studies, with grade 3–4 events occurring in 15–36% and 13–47% of patients, respectively. CPT-11, therefore, has significant activity in advanced colorectal cancer with response rates that are reproducible, durable and comparable to those achieved with 5-FU plus folinic acid in the first-line treatment of metastatic disease. Further work is needed to define the optimum dosage schedule for CPT-11 and also to assess fully the utility of CPT-11 in combination with other chemotherapeutic agents. Nevertheless, the activity of CPT-11 in patients refractory to treatment with 5-FU may be considered a significant advance, making it the first effective second-line agent in this setting. Copyright © 1996 Elsevier Science Ltd

Key words: CPT-11, phase II, colorectal cancer

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INTRODUCTION

THE POTENTIAL utility of CPT-11 (Campto®, irinotecan) as a new treatment for colorectal cancer was first recognised during the early development of the drug. Its novel and unique mechanism of action which involves inhibition of eukaryotic DNA-topoisomerase I [1, 2] was of particular interest since this enzyme is overexpressed in colorectal cancer cells [3]. In accord, CPT-11 demonstrated antitumour activity in preclinical studies against a variety of tumour colony-forming units, including cell lines of colorectal cancer [4] and those exhibiting multidrug resistance [5].

Phase I studies of CPT-11 conducted in Japan, Europe and the U.S. revealed diarrhoea and/or neutropenia to be the major dose-limiting toxicities of the drug [6–13]. However, different administration schedules were chosen for further investigation in each of these locations. This reflected differences in interpretation of study results and also the ability to administer higher CPT-11 doses with a once-every-3-weeks regimen in Europe which was facilitated by the use of loperamide to control delayed diarrhoea [14].

In the European phase I studies, 4 complete and 20 partial responses were reported in patients with a wide range of tumours [14]. The 6 partial responses with doses of CPT-11 $\geqslant 250$ mg/m^2 reported by Abigerges and colleagues in patients with colon cancer refractory to 5-fluorouracil (5-FU) were particularly encouraging [12]. These results were pivotal in the decision to formally assess the utility of CPT-11 in phase II studies of colorectal cancer. This review summarises the efficacy results of these phase II stu-

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Table 1. Principal eligibility criteria for patients with advanced colorectal cancer in phase II studies of CPT-11 in Japan, Europe and the U.S.

Criterion	Japan	Europe	U.S.
Histologically confirmed colorectal cancer	√	√	√
Progressive and/or measurable disease	√	√	√
Age (years)	⩽ 75	18–75	NA
ECOG or WHO performance status	⩽ 3	⩽ 2	⩽ 2
No chemotherapy or radiotherapy ⩽ 4 weeks before entry	√	—	√
⩽ 1 course of 5-FU-based therapy	—	√	—
Adequate bone marrow/haematological, liver, and renal function	√	√	√
No serious complications	√	√	—
No other active malignancies	√	—	—
Negative reaction to a CPT-11 skin test	√	—	—
Informed consent	√	√	√

NA, not available.

dies which were conducted in Japan, Europe and the U.S. These studies have previously been published either in their entirety [15, 16], or in preliminary form [17].

STUDY DESIGN, PATIENTS AND METHODS

All studies were conducted prospectively and had a non-randomised and open-label design. Their primary objective was to assess the clinical activity of CPT-11 in patients with advanced colorectal cancer, untreated or previously treated with chemotherapy. Objective tumour response rate was chosen as the primary efficacy end-point in all trials, although other assessments of efficacy included evaluation of response duration, disease progression and survival. In the Japanese and U.S. studies, duration of objective response was measured from the time of first observation of response; in the European study, response duration was calculated from the fist day of treatment, according to standard WHO criteria.

The principal eligibility criteria for patients entering these studies are provided in Table 1. In essence, only patients with histologically proven colorectal cancer, progressive/measurable disease and an ECOG or WHO performance status of ⩽ 2 (Europe, U.S.) or ⩽ 3 (Japan) were included. All patients were required to have adequate bone marrow/haematological, liver and renal function and all were required to provide informed consent prior to participation. The studies included both chemotherapy-naive and pre-treated patients. In the European study, patients were permitted to have received no more than one previous course of a 5-FU-based regimen and had to have a life expectancy of ⩾ 3 months.

Reflecting the different conclusions of phase I investigations, the CPT-11 dosage schedules employed in the three phase II studies varied. In Japan, patients were treated with a 90-min intravenous infusion of CPT-11 at a dosage of either 100 mg/m^2 every week or 150 mg/m^2 every 2 weeks. The U.S. investigators used a 6-week cycle of CPT-11 125 mg/m^2 administered once a week for 4 weeks followed by a 2-week break. However, in the last cohort of patients in this study ($n = 47$), the protocol was modified to allow (i) dose escalation to 150 mg/m^2 if patients experienced less than grade 2 toxicity; and (ii) repeat administration of the next course within 35 days if the prior week-4 infusion had been omitted. European investigators employed an intermittent CPT-11 regimen comprising a 30-min intravenous infusion administered at a dose of 350 mg/m^2 once every 3 weeks.

RESULTS FROM THE CLINICAL TRIALS

The demographic and clinical characteristics of patients recruited to each of the three studies are detailed in Table 2. A total of 359 patients with a median age of 57 to 66 years were evaluated. In the substantial majority of cases, ECOG or WHO performance status was ⩽ 1. Most patients presented with cancer of the colon rather than rectal cancer (data for Japan and Europe only) and metastases were most often identified in the liver and lung. With regard to prior treatment, almost all patients in the Japanese and European studies had undergone prior surgery, while 16 to 29% of patients in all three investigations had received radiotherapy. Of note, 74 to 81% of patients had previously been treated with chemotherapy, and 5-FU-based regimens were documented as being the most frequently used modality in two studies (Japan and Europe).

Measures of efficacy outcome from each of the studies are discussed in detail below and are summarised in Table 3.

Japan

In the Japanese investigation, 17 partial responses were recorded among 63 evaluable patients to give an overall response rate of 27% (95% confidence interval (CI) 16–38%). The response rates were 22.6% and 31.3% among patients treated with the weekly and bi-weekly schedules, re-

Table 2. Characteristics of patients with advanced colorectal cancer in phase II studies of CPT-11 in Japan, Europe and the U.S.

	Japan	Europe	U.S.
No. of patients enrolled	67	213	NA
No. of patients assessed	63	178	118
Median age in years (range)	57 (24–72)*	60 (18–76)	63–66 (32–82)*†
No. of males/females	37/26*	126/87	80/38*
ECOG or WHO performance status			
⩽ 1	46 (73%)*	184 (86%)	104 (88%)*
2	14 (22%)*	29 (14%)	14 (12%)*
3	3 (5%)*	—	—
Primary site			
Colon	38 (60%)*	151 (71%)	
Rectum	25 (40%)*	61 (29%)	
Metastatic site			
Liver	40 (63%)*	164 (77%)	54 (60%)‡
Lung	28 (44%)*	87 (41%)	45 (50%)‡
Lymph node	11 (17%)*	74 (35%)	
Peritoneum		38 (18%)	
Prior treatment			
Surgery	58 (92%)*	208 (98%)	
Radiotherapy	10 (16%)*	60 (28%)	34 (29%)*
Chemotherapy	51 (81%)*	165 (77%)	87 (74%)*
5-FU regimen	46 (73%)*	147 (69%)	
No chemotherapy	12 (19%)	48 (23%)	31 (26%)*
No of involved organs			
1		71 (33%)	42 (48%)‡
2		88 (41%)	35 (40%)‡
⩾ 3		52 (24%)	10 (11%)‡

* Data available for the assessed patients only; †For chemotherapy-naive and pretreated patients; ‡For pretreated patients only.
NA, not available.

spectively. The median duration of response was 208 days (6.8 months) and the median time to response 50 days. At sites of metastases, response rates were 15% for the liver, 39.3% for the lung and 36.4% for lymph nodes.

An important finding in this study was that CPT-11 showed activity in patients who had failed prior therapy with 5-FU based regimens. There were a total of ten partial responses among 46 such patients (response rate 21.7%), that persisted for a median duration of 163 days (5.4 months).

Treatment with CPT-11 was generally well tolerated, although the following grade 3 or 4 adverse events occurred: leucopenia (16% of patients), diarrhoea (13%), nausea and vomiting (13%) and alopecia (11%) [16].

Table 3. Efficacy outcome measures among patients with advanced colorectal cancer in phase II studies of CPT-11 in Japan, Europe and the U.S.

	Japan		Europe	U.S.
Dosage regimen	100 mg/m^2 weekly	150 mg/m^2 every 2 weeks	350 mg/m^2 every 3 weeks	125–150 mg/m^2 weekly
No. of evaluable patients	31	32	156	118
Overall response rate (95% CI)	22.6% (9.6–41.1)	31.3% (16.1–50.0)	20.5% (14.4–27.7)	17% (NA)
Response rate by pretreatment status (95% CI)				
Pretreated		21.7% (11.0–36.4)	20.0% (13.1–28.4)	14% (7–23)
Naive		NA	22.0% (10.5–37.6)	26% (12–45)
Median response duration* (95% CI)				
Overall		6.8 months (3.3–12.5)	9.1 months	NA
Pretreated patients		5.4 months	7.8 months	7.6 months (5–20)
Naive patients		NA	11.5 months	6.9 months (3–21)
Median survival duration				
Overall		NA	10.6 months	8.7 months
Pretreated patients		NA	10 months	8.3 months
Naive patients		NA	12 months	11.8 months

* Measured from the time of first observation of objective response in Japanese and U.S. studies, and from the start of study treatment in the European study.
NA, not available.

Europe

In the largest of the phase II studies conducted to date, in which patients were treated with CPT-11 once every 3 weeks, European investigators noted four complete and 28 partial responses, given an overall response rate of 20.5% (95% CI 14.4–27.7%) among evaluable patients ($n = 156$) and 18% (95% CI 12.6–24.4%) in the eligible patient population ($n = 178$). The median time to response was 9.3 weeks and median duration of response 9.1 months. Thirty-four per cent of patients were free from progression at 6 months and median overall survival was 10.6 months.

In accordance with the Japanese experience, CPT-11 again showed activity in patients refractory to treatment with other chemotherapeutic regimens. Indeed, the response rate was essentially similar among the chemotherapy-naive group (evaluable: 22.0%, 95% CI 10.5–37.6%; eligible: 18.8%, 95% CI 8.9–32.6%) and those previously treated with one 5-FU-based regimen (evaluable: 20.0%, 95% CI 13.1–28.4%, eligible: 17.7%, 95% CI 11.5–25.5%). In the latter group, the response rate was unaffected by the nature of prior chemotherapy (adjuvant or palliative). Furthermore, the similar response rates for patients who experienced early disease progression while receiving 5-FU (16.1% [eligible]; 95% CI 8.0–27.6%) and those who did not (19.1% [eligible]'; 95% CI 10.5–30.4%) suggest a lack of cross-resistance between CPT-11 and 5-FU. No significant difference was noted in the median time to response, median duration of response or median survival time when pretreated and chemotherapy-naive cohorts were compared. Progression-free survival at 6 months, however, favoured patients who had not been previously treated with chemotherapy (40 versus 32%).

Finally, response rates were highest in patients with a good performance status ($\leqslant 1$) and in those with $\leqslant 2$ organs involved.

As in the Japanese study, the most frequent grade 3 or 4 adverse events were leucopenia (33–36% of pretreated or chemotherapy-naive patients), delayed diarrhoea (35–39%), nausea and vomiting (13–22%) and alopecia (53–54%) [15].

U.S.A.

Using a weekly regimen similar to that employed in the Japanese study, U.S. investigators recorded an overall response rate of 17% (20 partial responses) among 118 evaluable patients. As with Japanese and European experience, prior chemotherapy did not preclude a response to CPT-11. Among the 88 pretreated patients, the response rate was 14% (95% CI 7–23%), median response duration 7.6 months and median survival 8.3 months. Furthermore, 57% of these patients experienced stable disease. Among the chemotherapy-naive cohort, the response rate was 26% (95% CI 12–45%) and median response duration 6.9 months. The disease state remained stable in 55% of patients and median survival was 11.8 months.

Diarrhoea was the major adverse event observed in this study, with grade 3 or 4 symptoms occurring in 17% and 30%, respectively, of the 30 patients assessable for toxicity. Grade 3 or 4 leucopenia occurred in 15% of patients [17].

CONCLUSION

Recent studies have demonstrated the beneficial effects of palliative chemotherapy on survival and well-being in patients with advanced colorectal cancer [18, 19]. 5-FU/folinic acid combinations have proved the most effective regimens to date, producing response rates typically of around 23% when used as first-line treatment [20]. However, in patients refractory to 5-FU monotherapy, response rates rarely exceed 10% [21]. There is, therefore, an obvious need for new effective chemotherapeutic agents for patients with advanced colorectal cancer, particularly for those with disease which is refractory to 5-FU.

Phase II investigations of CPT-11 have demonstrated this agent to possess significant activity in patients with advanced colorectal cancer. Overall response rates ranged from 17 to 27% and median duration of response from approximately 7 to 9 months. These values are comparable with response data for 5-FU plus folinic acid as first-line chemotherapy for patients with advanced colorectal cancer [20, 22, 23].

A remarkable characteristic of CPT-11 to emerge in these studies was its activity in patients refractory to other chemotherapeutic regimens, most notably those based on 5-FU. In this setting, modified schedules of 5-FU, including combination with modulating agents (e.g. folinic acid, methotrexate or interferon) or the use of prolonged or continuous infusions of 5-FU, have been investigated, but response rates have not exceeded 10–15% in most published trials [24].

The response rate to CPT-11 in patients refractory to prior chemotherapy ranged from 14 to 22% and endured for approximately 6 to 8 months (median). These findings are in accordance with the 25% response rate reported in a preliminary analysis of 44 patients treated with a weekly CPT-11 regimen as second-line therapy in the U.S. [25]. In the European study which only allowed entry to patients previously treated with $\leqslant 1$ 5-FU regimen, the response rate was essentially similar among pretreated and chemotherapy-naive patients. Further analysis of the latter group also suggested a lack of cross-resistance between CPT-11 and 5-FU.

Leucopenia and delayed diarrhoea were the major adverse events observed in these phase II studies. CPT-11-induced delayed diarrhoea can be particularly troublesome and, when associated with neutropenia, may increase the risk of infectious complications and related death. However, increasing experience with the use of CPT-11 has resulted in improvements in the control of delayed diarrhoea, and a review of the safety profile of CPT-11, based on experience from two consecutive European studies in patients with advanced colorectal cancer, has been presented by Bleiberg and Cvitkovic (pages S18–S23).

The above results support a pivotal role for CPT-11 in the treatment of patients with colorectal cancer and particularly those with disease refractory to 5-FU. Results from the European study suggest that performance status and degree of organ involvement will help in selecting the most appropriate patients for such therapy. Furthermore, as an appreciable proportion of patients were documented as having disease stabilisation with the drug in the European and U.S. investigations, it may well be of particular benefit in patients with progressive disease.

Given that the optimum administration schedules of established chemotherapeutic agents such as 5-FU have yet to be determined, despite several decades of clinical experience, it is to be expected that further investigations looking at the risk–benefit ratio of CPT-11 in advanced colorectal cancer are required before the optimum dosage schedule of this new compound can be fully defined. CPT-11 has shown consistent activity in phase II studies of colorectal cancer despite the use of different (weekly and intermittent) schedules. However, CPT-11 is an S-phase-dependent agent and *in vitro* studies suggest its activity is enhanced when low doses are administered for prolonged periods [27]. Administration of the drug by protracted intravenous infusion is, therefore, worthy of investigation.

In summary, CPT-11 as a single agent has demonstrated significant activity in advanced colorectal cancer with response rates that are reproducible, durable and comparable to those achieved with 5-FU plus folinic acid. Similar response rates have been achieved with CPT-11 when used as first- and second-line therapy in this setting, suggesting a lack of cross-resistance with 5-FU. Further work is needed to define the optimum dosage schedule for CPT-11 and to assess the utility of CPT-11 in combination with other chemotherapeutic agents. In the meantime, CPT-11 is likely to find particular use as the first effective agent in patients refractory to treatment with 5-FU.

1. Hsiang YH, Lihou MG, Liu F. Arrest of replication forks by drug-stabilised topoisomerase I–DNA cleavable complexes as a mechanism of cell killing by camptothecin. *Cancer Res* 1989, **49**, 5077–5082.
2. Tanizawa A, Fujimori A, Fujimori Y, Pommier Y. Comparison of topoisomerase I inhibition, DNA damage, and cytotoxicity of camptothecin derivatives presently in clinical trials. *J Natl Cancer Inst* 1994, **86**, 836–842.
3. Giovanella BC, Stehlin JS, Wall ME, *et al.* DNA-topoisomerase I-targeted chemotherapy of human colon cancer in xenografts. *Science* 1989, **246**, 1046–1048.
4. Shimada Y, Rothenberg M, Hilsenbeck SG, *et al.* Activity of CPT-11 (irinotecan hydrochloride): a topoisomerase inhibitor against human tumor colony-forming units. *Anticancer Drugs* 1994, **5**, 202–206.
5. Tsuruo T, Matsuzaki T, Matsushita M, *et al.* Antitumour effect of CPT-11, a new derivative of camptothecin, against pleiotropic drug-resistant tumors *in vitro* and *in vivo*. *Cancer Chemother Pharmacol* 1988, **21**, 71–74.
6. Taguchi T, Wakui A, Hasegawa K, *et al.* Phase I clinical study of CPT-11. *Jpn J Cancer Chemother* 1990, **17**, 115–120.
7. Negoro S, Fukuoka M, Masuda N, *et al.* Phase I study of weekly intravenous infusions of CPT-11, a new derivative of camptothecin, in the treatment of advanced non-small-cell lung cancer. *J Natl Cancer Inst* 1991, **83**, 1164–1168.
8. Ohe Y, Sasaki Y, Shinkai T, *et al.* Phase I study and pharmacokinetics of CPT-11 with 5-day continuous infusion. *J Natl Cancer Inst* 1992, **84**, 972–974.
9. Rothenberg ML, Kuhn JG, Burris HA, *et al.* Phase I and pharmacokinetic trial of weekly CPT-11. *J Clin Oncol* 1993, **11**, 2194–2204.
10. De Forni M, Bugat R, Chabot GG, *et al.* Phase I and pharmacokinetic study of the camptothecin derivative irinotecan, administered on a weekly schedule in cancer patients. *Cancer Res* 1994, **54**, 4347–4354.
11. Rowinsky EK, Grochow LB, Ettinger DS, *et al.* Phase I and pharmacological study of the novel topoisomerase I inhibitor 7-ethyl-10-(4-(1-piperidino)-1-piperidino)carbonyloxycamptothecin (CPT-11) administered as a ninety-minute infusion every 3 weeks. *Cancer Res* 1994, **54**, 427–436.
12. Abigerges D, Chabot GG, Armand J, *et al.* Phase I and pharmacologic studies of the camptothecin analog irinotecan administered every 3 weeks in cancer patients. *J Clin Oncol* 1995, **13**, 210–221.
13. Catimel G, Chabot GG, Guastalla JP, *et al.* Phase I and pharmacokinetic study of irinotecan (CPT-11) administered daily for three consecutive days every three weeks in patients with advanced solid tumors. *Ann Oncol* 1995, **6**, 133–140.
14. Armand J-P. CPT-11: clinical experience in phase I studies. *Semin Oncol*, 1996, **23**, 27–33.
15. Rougier P, Culine S, Bugat R, *et al.* A phase II study of CPT-11 (irinotecan) in the treatment of advanced colorectal cancer in chemotherapy-naive patients and patients pretreated with 5-FU-based chemotherapy. *J Clin Oncol*, in press.
16. Shimada Y, Yoshino M, Wakui A, *et al.* Phase II study of CPT-11, a new camptothecin derivative, in metastatic colorectal cancer. *J Clin Oncol* 1993, **11**, 909–913.
17. Pitot HC, Wender D, O'Connell MJ, *et al.* A phase II trial of CPT-11 (irinotecan) in patients with metastatic colorectal carcinoma: a North Central Cancer Treatment Group (NCCTG) study. *Proc Am Soc Clin Oncol* 1994, **13**, 197 (abstract 573).
18. Nordic Gastrointestinal Tumor Adjuvant Therapy Group. Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomized trial. *J Clin Oncol* 1992, **10**, 904–911.
19. Scheithauer W, Rosen H, Kornek G, *et al.* Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. *Br Med J* 1993, **306**, 752–755.
20. Advanced Colorectal Cancer Meta-Analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol* 1992, **10**, 896–903.
21. Cohen AM, Minsky BD, Schilsky RL. Colon Cancer. In DeVita Jr VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*, 4th edition. Philadelphia, JB Lippincott, 1993, 929–977.
22. Erlichman C, Fine S, Wong A, *et al.* A randomized trial of fluorouracil and folinic acid in patients with metastatic colorectal carcinoma. *J Clin Oncol* 1988, **6**, 469–475.
23. Petrelli N, Douglass HO, Herrera L, *et al.* The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma, a prospective randomized phase III trial. *J Clin Oncol* 1989, **7**, 1419–1426.
24. Adenis A. Les tumeurs gastro-intestinales. Compte-endus ASCO-AACR 1993. *Bull Cancer* 1993, **8**, 65S–72S.
25. Rothenberg ML, Eckardt JR, Burris III HA, *et al.* Irinotecan (CPT-11) as second line therapy for PTS with 5-FU-refractory colorectal cancer. *30th Annual Meeting of the American Society of Clinical Oncology*, 14–17 May, 1994. Dallas, Texas (abstract 578).
26. Bleiberg H, Cvitkovic E. Characterisation and clinical management of CPT-11 (irinotecan)-induced adverse events: the European perspective. *Eur J Cancer* 1996, **32A**(Suppl. 3), S18–S23.
27. Houghton PJ, Cheshire PJ, Hallman JC, *et al.* Therapeutic efficacy of the topoisomerase I inhibitor 7-ethyl-10-(4-[1-piperidino]-1-piperidino)-carbonyloxy-camptothecin against human tumor xenografts: lack of cross-resistance *in vivo* in tumors with acquired resistance to the topoisomerase I inhibitor 9-dimethylaminomethyl-10-hydroxycamptothecin. *Cancer Res* 1993, **53**, 2823–2829.