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A Risk-Benefit Assessment of Irinotecan in Solid Tumours

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Summary

Irinotecan is a water-soluble camptothecin analogue. Its cytotoxicity effects are exerted through interaction with the topoisomerase I–DNA complex, eventually leading to cell death.

In preclinical studies, irinotecan has demonstrated a broad spectrum of activity *in vitro* and *in vivo*, and synergistic effects have been observed when it is administered in combination with other antineoplastic agents.

Phase I studies of irinotecan conducted in Europe, Japan and the US have provided useful information on optimal dosage and scheduling, as well as thorough evaluation of the toxicity profile of the drug. Phase II and III trials utilising either irinotecan alone or in innovative combinations with other drugs are currently in progress. Available data indicate that irinotecan alone or in combination with other cytotoxic agents has therapeutic potential in several types of malignancy, including colorectal, lung, ovarian, cervical and gastric cancers and non-Hodgkin's lymphoma. It is the first drug since fluorouracil to possess consistent antitumour activity against metastatic colorectal cancer.

The principal toxicities associated with irinotecan are diarrhoea and leucopenia. Effective strategies have been developed to circumvent both the early- and

delayed-onset diarrhoea induced by irinotecan, thus allowing safer delivery of this promising agent in the clinical setting.

Camptothecin is a naturally occurring alkaloid isolated from the bark and wood of the Chinese tree *Camptotheca acuminata*.[1] Clinical development of this agent was halted when early studies demonstrated minimal antitumour activity along with unacceptable toxicities, namely haemorrhagic cystitis and toxic gastroenteritis.[2,3] In retrospect, the most likely cause of these toxic effects was the conversion of large amounts of the inactive soluble sodium salt (sodium camptothecin), that was used for administration, to the active lactone form in the acidic environments of the bladder and stomach.

Irinotecan (7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin) is a water-soluble analogue of camptothecin (fig. 1) that was synthesised initially by Yokokura and coworkers[4,5] at the Yakult Honsha Co. (Tokyo, Japan), in an attempt to improve on the therapeutic index of the parent compound.

While structural modifications to camptothecin have produced derivatives with variable clinical and pharmacological profiles, these drugs share a common molecular target – topoisomerase I. This primary target enzyme relaxes supercoiled double-stranded DNA arising during DNA replication and RNA transcription.[6-8] Torsional strain is relieved via the formation of a single-strand nick, followed by swivelling of the intact strand at the nick and subsequent religation. Camptothecin and its analogues act by stabilising the DNA/topoisomerase I 'cleavable complex,' thus preventing the religation of DNA strands. Irreversible damage probably results when an advancing DNA replication fork encounters the drug-stabilised cleavable complex, ultimately leading to lethal double-strand breaks and cell death.[9,10] As a consequence of their mechanism of action, the camptothecins are especially toxic to cells in the S phase of the cell cycle.[11,12]

Over the last decade, the discovery of a possible association between topoisomerase I expression and the malignant phenotype in some tumours[13,14] has also led investigators to realise that the camptothecins may be of significant use in oncological therapeutics.

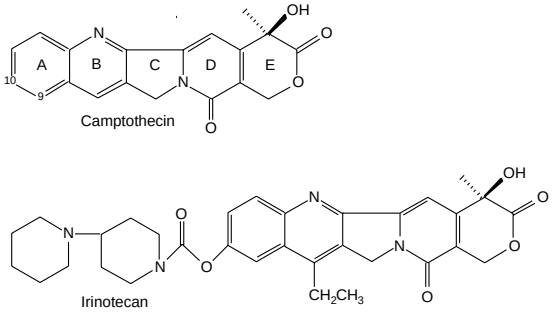

Fig. 1. Structure of camptothecin and irinotecan.

1. Bioactivation of Irinotecan

All camptothecins have a basic heterocyclic 5-ring structure with a lactone moiety and an α-hydroxyl moiety on the E ring (fig. 1). In general, substitutions at the C-9 or C-10 positions on the A ring tend to increase topoisomerase I inhibition, and sometimes aqueous solubility. Hence, the bulky piperidino side chain located at the C-10 position of irinotecan (fig. 1) produces enhanced therapeutic properties in comparison with the parent drug.[15] However, irinotecan itself is a prodrug with almost no inherent cytotoxicity, and cleavage of the piperidino side chain is necessary to generate a more biologically active entity. *In vivo*, irinotecan undergoes metabolic conversion by serum and tissue carboxylesterases to yield SN-38, an active metabolite which is 100- to 1000-fold more potent than irinotecan at inhibiting topoisomerase I activity.[16-20]

Similar to camptothecin and its other analogues, the closed lactone ring form of both irinotecan and SN-38 is reversibly hydrolysed to an open hydroxy acid (carboxylate) form, such that these substances exist as 2 distinct chemical species in solution. This

hydrolysis is pH-dependent, with the open-ring carboxylate form predominating at physiological pH. A dynamic equilibrium exists *in vivo* between the 2 forms so that an acidic environment shifts the reaction to the closed-ring form and a basic environment drives the equilibrium towards the inactive open-ring species.

The presence of an intact lactone ring is an essential structural requirement for cytotoxicity, since studies have suggested that the carboxylate form is a less potent inhibitor of topoisomerase I and a much less potent antitumour agent.[10,21] In fact, the carboxylate exerts its activities only by virtue of conversion to the lactone. Thus, a thorough pharmacokinetic analysis of irinotecan must take into consideration the total form and the lactone form of both the prodrug and SN-38.

2. Preclinical Evaluation of Irinotecan

2.1 *In Vitro* Activity

Irinotecan displays weak growth inhibitory activity against tumour cell lines *in vitro*, a phenomenon that is rectified by preincubation of the drug in serum. This modification of activity coincides with the formation of SN-38, confirming that the observed cytotoxicity is caused by the latter.[22] For instance, after 8 hours' exposure of HT-29 human colon carcinoma cells to various camptothecins, SN-38 demonstrated the greatest cytotoxic potency (see fig. 2).[23] Using freshly explanted tumours in the human tumour cloning assay, at final concentrations of 0.3 to 3.0 μg/ml and after a 1-hour exposure period, irinotecan demonstrated inhibitory activity against many tumour types, including colorectal, ovarian, non-small–cell lung (NSCLC) and breast cancer and mesothelioma.[24]

2.2 *In Vivo* Activity

When administered by the intraperitoneal, intravenous or oral route, irinotecan has shown significant antitumour activity in a broad spectrum of subcutaneously implanted murine tumour models. Probable cures were observed with S180 sarcoma, MethA fibrosarcoma, Lewis lung carcinoma, Ehrlich carcinoma, MH 134 hepatoma and mammary carcinoma of C3H/HeN mice.[25] The antitumour activity of irinotecan against intraperitoneally implanted L1210 leukaemia was superior to that of doxorubicin in several outcome parameters, including the maximum increase in life span (ILS), the number of cured mice and the therapeutic ratio.[25]

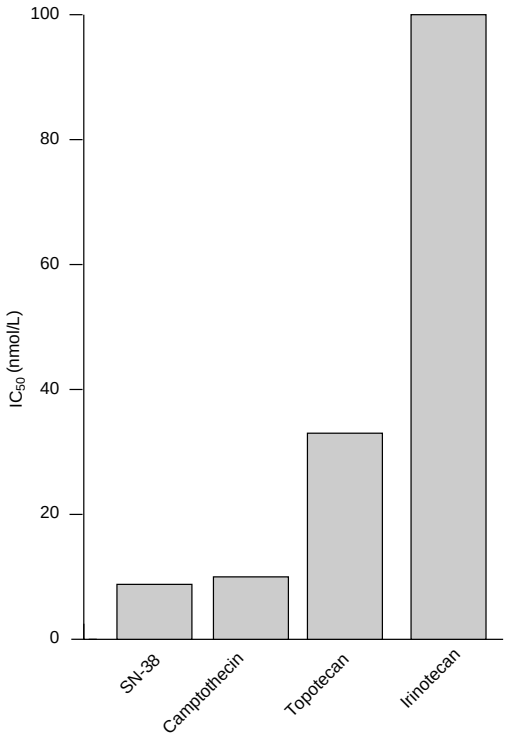

Fig. 2. Cytotoxic activity of camptothecins against HT-29 human colon carcinoma cells.[23] *Abbreviation:* IC_{50} = concentration of drug that was cytotoxic to 50% of cells.

Further confirmation of the cytotoxicity of irinotecan was evidenced by the finding that intravenous administration of the drug produced a T/C value (ratio of median weight of tumours from treated animals to median weight of tumours from control animals) of <10% in C51 colon adenocarcinoma, mammary 13C and 16C adenocarcinomas and PO3 pancreas adenocarcinoma. Tumour-free survivors were also observed in early stage PO3 pancreatic adenocarcinoma models.[22] Irinotecan

can also effectively inhibit spontaneous and experimental lung metastases of several highly metastatic variants of murine colon adenocarcinoma 16 and B16 melanoma.[26]

By using human tumour xenografts implanted subcutaneously in nude mice, irinotecan has demonstrated substantial tumour growth inhibitory activity against colon adenocarcinoma Co-4, mammary carcinoma MX-1, gastric adenocarcinoma St-15 and SC-6 and squamous cell lung carcinoma QG-56. In these tumour models, irinotecan produced results similar or superior to doxorubicin, cisplatin, fluorouracil and tegafur. Curative effects were noted in mice inoculated with mammary carcinoma MX-1, following intermittent intravenous injections of irinotecan given 4 days apart.[27]

Irinotecan was found to be effective in multidrug-resistant (MDR) tumour models, such as in vincristine- and doxorubicin-resistant P388 leukaemia-bearing mice.[28] The minimal recognition of irinotecan by the MDR phenotype makes this drug an ideal candidate for clinical development against tumours originating from tissues that constitutively express the mdr1 gene, such as colorectal cancer.[22] Excellent activity was also obtained in 1 study using irinotecan against juvenile and adult chemorefractory colon cancers, as well as childhood chemoresistant rhabdomyosarcoma sublines grown as xenografts in nude mice. Of interest was the observation that irinotecan was active against 2 xenografts (1 colon and 1 rhabdomyosarcoma) selected for primary resistance to topotecan, as it was against the respective parental tumours, suggesting a relative lack of cross-resistance between these topoisomerase I inhibitors.[29]

Irinotecan has been evaluated in preclinical experiments for synergistic or additive activity when given in combination with other antineoplastic agents. Using human lung tumour xenografts implanted in nude mice, the combination of irinotecan and cisplatin was shown to be superior to that of irinotecan or cisplatin alone.[30] Synergy between fluorouracil and irinotecan has also been demonstrated against several human colorectal cancer cell lines,[31,32] as well as against HT-29 human colon cancer[33] and L1210 murine leukaemia *in vivo*.[34] While concomitant administration of topoisomerase I and topoisomerase II inhibitors has generally resulted in antagonism and diminished cytotoxicity,[35] sequential combination of these inhibitors appears to lead to synergistic or additive effects.[36,37]

3. Irinotecan as a Single Agent

3.1 Phase I Trials

Phase I studies of irinotecan have been conducted in Japan, Europe and the US, using a variety of administration schedules: 90-minute infusion every week; 90-minute infusion every 2 weeks; 30- to 90-minute infusion every 3 weeks; 30- to 90-minute infusion daily for 3 days every 3 weeks; 60-minute infusion every 4 weeks; 120-minute continuous intravenous infusion every 3 to 4 weeks; 30- to 90-minute infusion weekly for 3 weeks followed by a 1-week rest period; 90-minute infusion weekly for 4 weeks followed by a 2-week rest period. The 2 schedules most frequently used in subsequent phase II studies of irinotecan are the 30- to 90-minute infusion every 3 weeks schedule and the 90-minute infusion weekly schedule with the drug given for 4 weeks followed by a 2-week drug-free interval.

3.1.1 Every 3 Weeks Schedule

Two phase I studies have evaluated the delivery of irinotecan by either a 30- or 90-minute intravenous infusion once every 3 weeks.[38,39] In the trial by Rowinsky et al.,[38] 90-minute infusions of irinotecan were administered every 3 weeks at doses ranging from 100 to 345 mg/m^2. 32 patients with solid malignancies received 144 total courses through 6 dose levels. Acute, severe and refractory vomiting, and diarrhoea and/or abdominal cramps associated with flushing, warmth and diaphoresis occurred in the immediate post-treatment period at the 240 mg/m^2 dose level in several patients, prompting the initiation of a premedication regimen consisting of ondansetron and diphenhydramine. With the routine use of these premedications, there was no single toxicity type that limited the

dose escalation of irinotecan. Instead, the dose-limiting toxicities observed were a constellation of severe haematological and nonhaematological toxicities, including severe, early- and/or delayed-onset abdominal cramps, diarrhoea, nausea, vomiting and anorexia, as well as prolonged severe neutropenia. The recommended phase II dose on this schedule was 240 mg/m^2. Major objective responses were seen in patients with advanced colorectal, cervical and renal cancers.

In the trial by Abigerges et al.,[39] irinotecan was likewise given once every 3 weeks, but over a shorter infusion time of 30 minutes. 64 patients were enrolled and received 190 total courses through 12 dose levels, ranging from 100 to 750 mg/m^2. Initially, irinotecan was always administered without any prophylaxis for nausea or vomiting, but anti-emetic therapy with alizapride and dexamethasone, or ondansetron, was allowed during subsequent cycles.

Diarrhoea appeared dose-limiting at 350 mg/m^2, but this toxicity was functionally circumvented by using a high-dose loperamide protocol that allowed further dose escalation. Patients were instructed to take 2mg of loperamide every 2 hours at the first diarrhoeal episode, and were allowed to stop loperamide only after a 12-hour diarrhoea-free interval, in relation to the last diarrhoeal episode. With the implementation of this protocol, diarrhoea was no longer dose-limiting, and neutropenia was consequently the principal toxicity in this study. The recommended phase II dosage was 350 mg/m^2 every 3 weeks for safety reasons, since diarrhoea was a significant clinical problem at that level, albeit controllable with anti-diarrhoeal therapy. The authors suggested a higher dose of 500 mg/m^2 in good-risk patients, when careful monitoring of gastrointestinal toxicities is feasible.

Complete responses were observed in 2 patients (one with cervical cancer and the other with head and neck cancer) who had been pretreated with fluorouracil and cisplatin (CDDP). Partial responses were documented in 6 patients with fluorouracil-refractory colon adenocarcinoma. The current recommended and approved initial dosage of irinotecan in Europe, where the once every 3 weeks regimen is commonly used, is 350 mg/m^2 administered as a 30- to 90-minute intravenous infusion.

3.1.2 Weekly for 3 or 4 Weeks Over a 6-Week Cycle Schedule

In the US and Japan, the preferred treatment regimen is 1 dose of irinotecan administered weekly for 4 weeks followed by a 2-week rest interval. The recommended initial dose for this schedule was derived from 2 phase I studies, one conducted by Rothenberg et al.[40] in the US, and the other by Negoro et al.[41] in Japan.

In the study reported by Rothenberg et al.,[40] 32 patients were treated with irinotecan given as a 90-minute intravenous infusion every week for 4 consecutive weeks, followed by a 2-week rest period. Dose levels ranged from 50 to 180 mg/m^2/week, and delayed onset diarrhoea was found to be dose-limiting. Early recognition of this toxicity and intervention using antimotility agents such as loperamide or diphenoxylate-atropine were advocated. However, once grade 4 diarrhoea occurred, no pharmacological measures were found to be effective in arresting or reversing this process. The focus of management was primarily supportive with intravenous fluid and electrolyte replacement until the episode resolved, generally within 5 to 7 days. Haematological toxicity was mild in most patients, with grade 4 neutropenia observed in only 1 of 32 patients (3.1%) during the first cycle. Partial responses were seen in 2 patients who had recurrent colorectal cancer.

The recommended phase II dosage from this trial was 150 mg/m^2/week. However, in the subsequent US phase II study of irinotecan in patients with progressive or rapidly recurrently colorectal cancer,[42] this starting dosage was found to be too toxic, with 4 of the first 9 patients (44%) developing grade 4 diarrhoea and severe dehydration during the first treatment cycle. Hence, the starting dosage was reduced to 125 mg/m^2/week for 4 weeks every 6 weeks, which is the current approved dosage for irinotecan in the US.

Table I. Phase II studies of irinotecan in patients with metastatic colorectal cancer

Reference	Prior chemotherapy	Treatment dose (mg/m^2) and schedule	No. of evaluable patients	Effect				
				response rate (%)	median duration of response (mo)	median survival (mo)	grade 3/4 diarrhoea (% of patients)	grade 3/4 leucopenia (% of patients)
Shimada et al.[47]	In 81% (73% with fluorouracil)	100 q1wk or 150 q2wk	63	17/63 (27.0)	6.8		12.9	16.1
Rothenberg et al.[42]	Fluorouracil-based (× 1)	125-150 q1wk × 4, over a 6wk cycle	43	10/43 (23.2)	6	10.4	37.5	25.0
Pitot et al.[48]	Fluorouracil-based (× 1)	125-150 q1wk × 4, over a 6wk cycle	90	12/90 (13.3)	7.7	8.3	36.4[a]	21.5[a]
Van Cutsem et al.[49]	Fluorouracil-based (× 1)	350 q13wk	95	13/95 (13.7)			25[b]	
Rougier et al.[50]	Fluorouracil-based (× 1)	350 q3wk	130	23/130 (17.7)	9.1[a]	11.5	39	35
Pitot et al.[48]	None	125-150 q1wk × 4, over a 6wk cycle	31	8/31 (25.8)	7.6	11.8	36.4[a]	21.5[a]
Conti et al.[51]	None	125-150 q1wk × 4, over a 6wk cycle	41	13/41 (31.7)	8.1	12.1	29.3	12.2
Rougier et al.[50]	None	350 q3wk	48	9/48 (18.8)	9.1[a]	12	35	36

a Separate values not provided for chemotherapy-naive patients versus those who had fluorouracil based chemotherapy.

b Based on 79 patients.

Abbreviation: q*x*wk = every *x* weeks.

ferent administration schedules in metastatic colorectal cancer.

Among approximately 420 patients with fluorouracil-refractory disease, the response rates ranged from 13 to 27%.[42,47-50] Response rates were slightly higher among 120 newly diagnosed chemotherapy-naive patients who received the drug, ranging from 19 to 32%.[48,50,51] The median durations of response were generally 6 to 9 months, and were similar in the 2 patient populations.

A recent combined analysis[52] of 304 US patients with previously treated metastatic colorectal cancer revealed no correlation between response to irinotecan and response to prior fluorouracil. A number of significant positive predictors of response in these patients were identified: (i) good performance status; (ii) prior fluorouracil given for metastatic disease rather than as an adjuvant; and (iii) the occurrence of first-course diarrhoea. Almost half of the patients achieved disease stabilisation, often with tumour reductions that did not meeting formal partial response criteria. Survival outcome was consistent among all reported phase II trials: the median survival was about 9 months for patients who had received one prior fluorouracil-based regimen, whereas the median survival was about 12 months for those who received irinotecan as their first line of therapy.

Not surprisingly, diarrhoea was commonly observed in all studies. By combining the toxicity data from over 500 patients in all phase II studies, the incidence of grade 3 or 4 diarrhoea was about 32%. Many of the studies adopted and specified a standardised approach to treatment of both the acute-onset and delayed-onset types of diarrhoea associated with irinotecan, although minor variations existed between different institutions. Generally, an anticholinergic agent was used to ameliorate the symptoms of acute-onset diarrhoea, while an aggressive loperamide protocol was applied to control and arrest those of delayed-onset diarrhoea. Leucopenia was the other principal toxicity noted in these studies: its frequency appeared to correlate with the schedule of irinotecan administration. The European schedule of once every 3 weeks produced grade 3 or 4 leucopenia in about 35% of patients, while the US schedule of weekly therapy for 4 weeks followed by a 2-week rest may be less myelotoxic and produced grade 3 or 4 leucopenia in about 20% of patients.

Irinotecan has emerged as one of the few chemotherapeutic agents with activity in metastatic colorectal cancer, seemingly comparable to fluorouracil. Studies evaluating its use in combination regimens are ongoing (see section 4).

3.2.2 Lung Cancer

The vast majority of phase II studies of irinotecan in lung cancer have been performed in Japan, where it is now approved for the treatment of NSCLC and small-cell lung cancer (SCLC). Confirmatory trials evaluating the activity of this drug as a single agent in these tumour types are being conducted in Europe and the US.

Table II summarises the results of clinical studies that have investigated the effects of irinotecan alone in different administration schedules in patients with NSCLC and SCLC.[53-59] In NSCLC, irinotecan has no activity in patients who had received prior chemotherapy, whereas response rates of 15 to 36% were obtained in chemotherapy-naive patients. In contrast, both previously treated and untreated SCLC demonstrated chemosensitivity to irinotecan. Response rates of 16 to 47% were seen in SCLC patients who had prior cisplatin-based chemotherapy, and 1 study reported a complete response in a patient with brain metastasis.[59] Only 1 study of SCLC included chemotherapy-naive patients,[54] and responses were noted in 4 of 8 patients (50%).

Diarrhoea and myelosuppression were the principal toxicities associated with irinotecan administration. Two of the studies[56,58] described treatment-related moderate to severe pulmonary toxicity, although the effects of disease progression and radiation were potentially confounding. In the study of NSCLC by Fukuoka et al.,[56] 6 of 72 patients (8%) developed pulmonary toxicity and 1 patient died of respiratory failure. In the study of SCLC by Masuda et al.,[58] 2 of 15 patients (13%) experienced grade 3 or 4 pulmonary toxicity and 1

Table II. Phase II studies of irinotecan in patients with lung cancer

Reference	Prior chemotherapy	Treatment dose (mg/m^2) and schedule	No. of evaluable patients	Effect				
				response rate (%)	median duration of response (mo)	median survival (mo)	grade 3/4 diarrhoea (% of patients)	grade 3/4 leucopenia (% of patients)
Non–small-cell lung cancer								
Nakai et al.[53]	Yes/no	200 q3-4wk	35	7/35 (20)			13[a]	18[a]
Negoro et al.[54]	Yes	100 q1wk	26	0/26 (0)			18[a]	25[a]
	No		67	23/67 (34.3)				
Baker et al.[55]	No	100 q1wk × 4, over a 6wk cycle	41	6/41 (14.6)	4.7	6.2	16.7	10.4
Fukuoka et al.[56]	No	100 q1wk	72	23/72 (31.9)	3.5	9.7	21	25
Douillard et al.[57]	No	350 q3wk	11	4/11 (36)			26	42[b]
Small-cell lung cancer								
Nakai et al.[53]	Yes/no	200 q3-4wk	3	1/3 (33)			13[a]	18[a]
Negoro et al.[54]	Yes	100 q1wk	27	9/27 (33.3)			18[a]	25[a]
	No		8	4/8 (50)				
Le Chevalier et al.[59]	Etoposide/cisplatin-based regimen (× 1)	350 q3wk	31	5/31 (16)	4.3	4.1	37	58[b]
Masuda et al.[58]	Yes	100 q1wk	15	7/15 (47)	1.9	6.1	7	33

a Separate values not provided for non–small-cell lung cancer and small-cell lung cancer.

b Grade 3/4 neutropenia.

Abbreviation: qxwk = every *x* weeks.

Table III. Phase II studies of irinotecan in patients with various malignancies

Reference	Prior chemotherapy	Treatment dose (mg/m^2) and schedule	No. of evaluable patients	Effect				
				response rate (%)	median duration of response (mo)	median survival (mo)	grade 3/4 diarrhoea (% of patients)	grade 3/4 leucopenia (% of patients)
Ovarian								
Takeuchi et al.[60]	Yes/no	100 q1wk or 150 q2wk	55	13/55 (24)				
Cervical								
Takeuchi et al.[60]	Yes/no	100 q1wk or 150 q2wk	55	13/55 (24)				
Potkul et al.[61]	Yes (platinum-resistant)	125 q1wk × 4, over a 6wk cycle	14	0/14 (0)			21	43
Verschraegen et al.[62]	Yes (1-4 regimens)	125-150 q1wk × 4, over a 6wk cycle	42	9/42 (21)	2.8	6.4	24	31
Chevallier et al.[63]	No	350 q3wk	34	5/34 (15)	>5.5			26[a]
Breast								
Taguchi et al.[64]	Yes/no	100 q1wk	65	15/65 (23)			11	30
Bonneterre et al.[65]	Yes	350 q3wk	12	1/12 (8)				
Pancreatic								
Sakata et al.[66]	Yes/no	100 q1wk or 150 q2wk	35	4/35 (11)			23	39
Wagener et al.[67]	No	350 q3wk	32	3/32 (9)	7.5	5.2	21	50
Gastric								
Futatsuki et al.[68]	Yes/no	100 q1wk or 150 q2wk	60	14/60 (23)			22	42
Leukaemia (leu) and lymphoma (lym)								
Ohno et al.[69]	No	200 q3-4wk 40/day × 5 q3-4wk 40/day × 3 q1wk 20 bid × 7 q3-4wk	10 25 9 14	0% for both 0% in leu; 5/16 (31) in lym 0% in leu; 3/8 (38) in lym 3/12 (25) in leu; 0% in lym				Lym without bone marrow involvement: 71[b]

a Grade 3/4 neutropenia.

b Overall for all 4 regimens.

Abbreviations: bid = twice daily; q*x*wk = every *x* weeks.

Table IV. Phase I studies of irinotecan (IRI) in combination with other cytotoxic agents

Reference	Tumour type	Drugs and treatment schedule	No. of evaluable patients	Recommended phase II dose (mg/m^2)	Dose-limiting toxicity	Other toxicities	Responses
Shimada et al.[70]	CRC	IRI day 1 and FU days 1-7 by continuous infusion, q3-4wk	21	Not yet defined	Not reached at IRI dose of 200 mg/m^2		PR in 3/15 assessable pts (20%)
Benhammouda et al.[71]	Solid tumours, majority with CRC (29/41)	IRI day 0 or 6 and FU days 1-5 by IV bolus, q4wk	41	IRI: 300 (no difference for day 0 *vs* day 6) FU: 375/day	Haematological		
Saltz et al.[72]	Solid tumours, majority with CRC (38/41)	IRI, FU and CF q1wk × 4, for a 6wk cycle	41	IRI: 125 FU: 500 CF: 20	Neutropenia	3 pts had grade 3/4 diarrhoea	PR in 6/35 assessable CRC pts (17%)
Parnes et al.[73]	Solid tumours, CRC (4/9)	IRI wk 1 and 4, FU and CF q1wk × 4, for a 6wk cycle	9	IRI: 25 FU: 500 CF: 500	Diarrhoea	1 pt had grade 3/4 neutropenia	No responses observed
Rougier et al.[74]; Ducreux et al.[75]	CRC	IRI day 1, followed by De Gramont regimen[a] days 1 and 2, q2wk	30	Not yet defined	Not reached at IRI dose of 200 mg/m^2		CR in 1/20 and PR in 4/20 assessable pts (25%)
Karato et al.[77]	Solid tumours, majority with lung cancer (21/33)	IRI and ETO days 1-3, q3-4wk + G-CSF on days 4-17	33	IRI: 60 ETO: 60 G-CSF: 50 $\mu g/m^2$/day	Diarrhoea	18 pts had grade 3/4 neutropenia	PR in 10/22 assessable pts (NSCLC, HNC, ACUP)
Saltz et al.[78]	Solid tumours	IRI and CIS q1wk × 4, for a 6wk cycle	8	IRI: 50 CIS: 30 (PT)	Neutropenia		PR in 3/8 (38%)
Masuda et al.[79]	NSCLC (9/21) SCLC (12/21)	IRI days 1, 8 and 15, and ETO days 1-3, q4wk + G-CSF on days 4-21	21	IRI: 80 mg/m^2 (PU) and 70 (PT) ETO: 80 G-CSF: 2 g/kg/day	Neutropenia and diarrhoea	Moderate thrombocytopenia	NSCLC: PR in 2/9 (22%) SCLC: CR in 1/12 and PR in 6/12 (50%)
Masuda et al.[80]	NSCLC	IRI days 1, 8 and 15, and CIS day 1, q4wk	26	IRI: 60 CIS: 80	Neutropenia and diarrhoea	Mild anaemia, nausea and vomiting	PR in 14/26 (54%)
Masuda et al.[81]	NSCLC (12/14) SCLC (2/14)	IRI days 1, 8 and 15, and CIS day 1, q4wk	14	IRI: 80 CIS: 60	Diarrhoea	5 pts had grade 3 leucopenia	NSCLC: responses in 4/12 (33%) SCLC: responses in 2/2 (100%), 1 CR noted (histological type unspecified)
Ueoka et al.[82]	NSCLC (12/16) SCLC (4/16)	IRI and CIS days 1 and 8, q4wk	16	IRI: 50 CIS: 60	Leucopenia and diarrhoea		NSCLC: PR in 12/16 (75%) SCLC: PR in 4/4(100%)
Kobayashi et al.[83]	NSCLC	IRI and CIS days 1, 8 and 15, q4wk	18	IRI: 60 CIS: 33	Leucopenia	1 pt had grade 3 diarrhoea	PR in 5/7 assessable pts (71%)

table IV contd

bination of irinotecan and cisplatin in this malignancy.

Irinotecan has been evaluated in at least 1 study of haematological malignancies. Using 4 different treatment schedules, Ohno et al.[69] conducted a multi-institutional Japanese cooperative phase II study of irinotecan in 62 patients with refractory leukaemia and lymphoma. Infusions of 60-minutes duration at a dosage of 40 mg/m^2/day for 5 days every 3 to 4 weeks or for 3 days weekly produced 4 complete and 4 partial responses, or an overall response rate of 33%, in 24 patients with malignant lymphoma. A dosage of 20 mg/m^2 twice a day, given as 60-minute infusions, for 7 days every 3 to 4 weeks resulted in 1 complete and 2 partial responses, or an overall response rate of 25% in 12 patients with acute leukaemia. Major adverse effects were leucopenia and diarrhoea. From this study, it appeared that schedules allowing prolonged exposure of irinotecan were the most effective in these haematological malignancies.

4. Irinotecan Given in Combination with Other Cytotoxic Agents

4.1 Phase I Trials

Since the establishment of its activity as a single agent in a broad spectrum of tumour types, a large number of initial phase I studies of irinotecan in combination with other cytotoxic drugs have been conducted (table IV). Logical choices of drugs to be administered in combination with irinotecan are those with different mechanisms of action and toxicity profiles, as well as those for which there is preclinical evidence of additivity or synergy when given together with irinotecan. Fluorouracil, cisplatin and etoposide are among the most frequently selected drugs delivered in combination with irinotecan in the various published phase I studies using different administration schedules.

4.1.1 Irinotecan and Fluorouracil

The feasibility of combining irinotecan and fluorouracil with or without calcium folinate (leucovorin) has been evaluated by several groups.[70-75] While the synergistic interaction of irinotecan and

Masuda et al.[84]	NSCLC	IRI days 1, 8 and 15, and CIS day 1, q4 wk + G-CSF days 4-21	20	IRI: 80 CIS: 80 G-CSF: 2 μg/kg/day	Diarrhoea	3 pts had grade 3/4 leucopenia	PR in 10/20 (50%)
Mori et al.[85]	NSCLC	IRI day 1, andCIS days 1-5 by continuous infusion, q4wk	20	IRI: 80 CIS: 20/day	Neutropenia	2 pts had grade 3/4 diarrhoea	PR in 9/19 assessable pts (47%)
Shinkai et al.[86]	NSCLC	IRI and VIN days 1 and 8, and CIS days 1, q3-4wk	46	IRI: 37.5 VIN: 3 CIS: 100 or IRI: 80 VIN: 3 CIS: 60	Neutropenia and diarrhoea	3 pts had grade 3 liver toxicity	PR in 15/33 assessable pts (45%)
Shirao et al.[87]	Gastric cancer	IRI day 1 and 15, and CIS day 1, q4wk	24	IRI: 70 CIS: 80/day	Neutropenia	3 pts had grade 3/4 diarrhoea	PR in 10/24 (42%)

a Calcium folinate (leucovorin) at 200 mg/m^2 and fluorouracil bolus at 400 mg/m^2 on day 1, followed by fluorouracil 22h intravenous infusion at 600 mg/m^2 on days 1 and 2.

Abbreviations: ACUP = adenocarcinoma of unknown primary; CF = calcium folinate; CIS = cisplatin; CR = complete response; CRC = colorectal cancer; ETO = etoposide; FU = fluorouracil; G-CSF = granulocyte colony-stimulating factor; HNC = head and neck cancer; IV = intravenous; LV = leucovorin; NSCLC = non–small-cell lung cancer; PR = partial response; PT = for previously treated patients; PU = for previously untreated patients; qxwk = every *x* weeks; SCLC = small-cell lung cancer; VIN = vindesine.

fluorouracil in the preclinical setting (see section 2.2) makes their co-administration an attractive option, their similar adverse effect profile is a realistic concern.

Shimada et al.[70] were the first investigators to combine these agents, in a phase I study where escalating doses of irinotecan were given as a 90-minute infusion on day 1, followed by continuous infusion of fluorouracil given at a fixed dosage of 400 mg/m^2/day for 7 days, in 3- or 4-week treatment cycles. Toxicities observed at irinotecan doses up to 200 mg/m^2 were not dose-limiting and consisted primarily of mild to moderate, but controllable, nausea/vomiting and diarrhoea. At the time of the report, patient accrual continued to define the recommended phase II dose on this schedule. Pharmacokinetic analysis was performed in a proportion of patients taking this combination regimen.[76] Interestingly, the area under the plasma concentration-time curve (AUC) for irinotecan was higher in this group of patients than that of a historical control group who received similar doses of irinotecan alone. In contrast, however, the AUC for SN-38 was much lower in the group treated with the combination than in the control group. These observations led to the speculation that fluorouracil, or its metabolite, may inhibit the activity of carboxylesterase.

Saltz et al.[72] subsequently performed rigorous pharmacokinetic evaluations in a larger group of patients who received irinotecan and fluorouracil plus calcium folinate in different sequences, so that each patient served as his or her own internal control for concentrations of irinotecan and SN-38. The conclusion drawn from this study was that fluorouracil does not substantially affect the metabolism of irinotecan to its active metabolite SN-38.

In the French study by Benhammouda et al.,[71] irinotecan was given as a 30-minute intravenous infusion in escalating doses either 1 day before (day 0) or 1 day after (day 6) a 5-day course of daily injections of fluorouracil, in alternate 4-week cycles. The dose-limiting toxicity was haematological, and delayed diarrhoea requiring intravenous rehydration occurred in only 8 of 138 assessable cycles of chemotherapy. The recommended phase II doses on this schedule were irinotecan 300 mg/m^2 and fluorouracil 375 mg/m^2/day, with no difference observed between the 2 orders of administration.

In the US study by Saltz et al.,[72] irinotecan, fluorouracil and low-dose calcium folinate were given in repeated 6-week cycles that consisted of weekly treatment with all 3 drugs for 4 consecutive weeks, followed by a 2-week break. The dose of calcium folinate was fixed in this study, with initial dose escalations of fluorouracil and subsequent dose escalations of irinotecan. Neutropenia was the major dose-limiting toxicity, while diarrhoea was common but rarely severe. The combination of irinotecan 125 mg/m^2, fluorouracil 500 mg/m^2 and calcium folinate 20 mg/m^2 was tolerable on this schedule and was recommended for phase II administration.

Although the above study demonstrated the feasibility of concurrent administration of substantial doses of fluorouracil and irinotecan, other investigators have reported less favourable outcomes when using this combination. Parnes et al.[73] administered irinotecan on weeks 1 and 4 of each 6-week cycle, combined with fluorouracil and high-dose calcium folinate given weekly on weeks 1 to 4. This combination resulted in formidable toxicity. Dose-limiting diarrhoea developed early in the course of this clinical trial. Only 25 mg/m^2 of irinotecan could be delivered safely with fluorouracil 500 mg/m^2 and calcium folinate 500 mg/m^2 on this schedule. While the slight variation in treatment schedule in this study may have altered the toxicity profile of the drug combination, the use of high-dose instead of low-dose calcium folinate may also have potentiated the occurrence of diarrhoea.

At present, a phase III randomised, controlled, multicentre trial is ongoing, comparing irinotecan alone, fluorouracil plus calcium folinate, and combined irinotecan and fluorouracil plus calcium folinate in patients with untreated metastatic colorectal cancer. The combined therapy arm in this study is based on the aforementioned protocol

tested by Saltz et al.[72] In Europe, a phase I/II study of combined therapy in patients with fluorouracil-resistant colorectal cancer is ongoing,[74,75] with increasing doses of irinotecan given as a 90-minute infusion on day 1 before the De Gramont regimen (calcium folinate at 200 mg/m^2 and fluorouracil bolus at 400 mg/m^2 on day 1, followed by a 22-hour intravenous infusion of fluorouracil at 600 mg/m^2 on days 1 and 2), repeated every 2 weeks.

4.1.2 Irinotecan and Etoposide

Two Japanese phase I studies[77,79] have evaluated the combination of irinotecan and etoposide, both using growth factor support because myelosuppression, especially leucopenia, is the principal dose-limiting toxicity common to these 2 agents.

In the study by Karato et al.,[77] patients with refractory solid tumours, including a large proportion with lung primaries, received irinotecan and etoposide daily for 3 consecutive days every 3 or 4 weeks. Recombinant human granulocyte colony-stimulating factor (G-CSF) was administered at a dosage of 50 μg/m^2/day on days 4 to 17. The dose-limiting toxicity was diarrhoea, and despite the use of G-CSF, a considerable number of patients experienced grade 3 or 4 neutropenia. The recommended phase II doses of irinotecan and etoposide were both 60 mg/m^2 on this schedule. Partial responses were achieved in patients with NSCLC, head and neck cancer and adenocarcinoma of unknown primary, but no complete responses were observed.

In the study by Masuda et al.,[79] patients with advanced lung cancers were treated in 4-week cycles with irinotecan on days 1, 8 and 15, and with etoposide on day 1 to 3. Again, the use of G-CSF was mandatory and daily subcutaneous injections were given from days 4 to 21 of each cycle, except on the days of irinotecan administration. Diarrhoea and leucopenia were the dose-limiting adverse effects, suggesting that even prophylactic therapy with G-CSF cannot completely compensate for the haematological toxicity of these drugs. Grade 2 pneumonitis, which resolved with corticosteroid therapy, was seen in 1 patient treated with irinotecan 60 mg/m^2 during the third course. The response rate among 9 assessable patients with NSCLC was 22%, with 2 partial responses, both of which occurred in chemotherapy-naive patients. Among 12 assessable patients with SCLC, the overall response rate was 58%. Of the 11 patients who had received prior therapy, 1 achieved a complete response and 5 achieved partial responses. The remaining 1 patient who had not received prior therapy attained a partial response. The recommended phase II doses on this schedule were irinotecan 80 mg/m^2 for previously untreated patients and 70 mg/m^2 for previously treated patients, along with etoposide 80 mg/m^2. It appeared that, when compared with the concomitant administration of both drugs for 3 consecutive days, similar dose intensities of both drugs could be maintained with the combination of monthly etoposide and weekly irinotecan.

4.1.3 Irinotecan and Cisplatin

The combination of irinotecan with cisplatin has been comprehensively tested in dose-finding studies in patients with refractory solid tumours,[78] advanced lung cancer[80-86] and gastric cancer.[87] The rationale for these efforts are multifold, including the synergy between these 2 agents in preclinical models, their impressive cytotoxic activity when administered individually against a wide range of tumours, and their non-overlapping principal toxicities.

In 3 of the studies, split doses of irinotecan and cisplatin were given together as weekly treatments followed by a rest period. Administration schedules that were explored included weekly for 2 weeks over a 4-week cycle,[82] weekly for 3 weeks over a 4-week cycle,[83] and weekly for 4 weeks over a 6-week cycle.[78] The recommended phase II doses of irinotecan/cisplatin for these 3 schedules were: 50/60, 60/33 and 50/30 mg/m^2, respectively. Myelosuppression in the form of leucopenia or neutropenia was dose-limiting in all cases, and diarrhoea was also dose-limiting on the weekly-times-two every 4 weeks schedule. No pulmonary toxicity was reported. Two of the studies[82,83] involved patients with NSCLC and both reported partial responses in 71 and 75% of patients; how-

Table V. Phase II studies of irinotecan (IRI) in combination with other cytotoxic agents

Reference	Prior chemotherapy	Treatment dose (mg/m^2) and schedule	No. of evaluable patients	Effect				
				response rate (%)	median duration of response (mo)	median survival (mo)	grade 3/4 diarrhoea (% of patients)	grade 3/4 leucopenia (% of patients)
Colorectal cancer								
Rothenberg et al.[88]	None	IRI 100 q1wk × 4, q6wk alternating with FU 425 and CF 20 days 1-5, q4wk	70	18/70 (26)	7.1		IRI: 15.7 FU and CF: 4.6	Grade 3/4 neutropenia IRI: 5.7 FU and CF: 1.5
Barone et al.[89]	None	IRI 350 q3wk alternating with FU 425 and CF 20 days 1-5, q3-4wk	19	4/19 (21)				
Non–small-cell lung cancer								
Oshita et al.[90]	None	IRI 60 and ETO 60 days 1-3, q3wk + G-CSF 50g/m^2/day on days 4-17	61	13/61 (21.3)	4.6	10.0	16	23
DeVore et al.[91]	Not specified	IRI 60 days 1, 8 and 15, and CIS 80 day 1, q4 wk	52	16/52 (31)	3.4	8.4	17	23
Mori et al.[92]	None	IRI 160 day 1, and CIS 20/day on day 1-5 by continuous infusion, q4wk, + G-CSF	41	22/41 (54)			25	13
Saka et al.[93]	None	IRI 60 q1wk × 6wk and concurrent thoracic XRT 60 Gy/30 fractions/6wk	24	19/24 (79)			0	4
Kudoh et al.[94]	No	IRI 60 days 1, 8,15 and CIS 60 day 1, q4wk	LD: 40 ED: 35	LD: 33/40 (83%) ED: 30/35 (86%)	LD: 8.0 ED: 6.6	LD: 14.3 ED: 13.0	19	45
Ovarian								
Sugiyama et al.[95]	Not specified	IRI 50-60 days 1, 8 and 15, and CIS 50-60 day 1, q4wk	11	6/11 (54.5)				Grade 3/4 neutropenia ≥50%
Shimizu et al.[96]a	Yes/no	IRI 140 and MIT-C IP 7 days 1, 15 and 29, q4wk	20	12/20 (60)				
Gastric								
Boku et al.[97]	≤ One regimen	IRI 70 days 1 and 15, and CIS 80 day 1, q4wk	44	Overall: 21/44 (48) Previously untreated patients: 17/29 (59)	3.9	10.2	7% of all courses	Grade 4 neutropenia in 22% of all courses

a Clear cell adenocarcinoma of ovary.

Abbreviations: CF = calcium folinate (leucovorin); CIS = cisplatin; ED = extensive disease; ETO = etoposide; FU = fluorouracil; G-CSF = granulocyte colony-stimulating factor; IP = intraperitoneal injection; LD = limited disease; MIT-C = mitomycin C; XRT = radiation.

ever, complete responses were not noted. One study[82] tested this drug combination in 4 evaluable patients with SCLC and reported a partial response rate of 100%.

Using a different treatment schedule, Masuda et al.[80,81,84] conducted 2 dose-escalation combination studies of irinotecan and cisplatin in patients with advanced lung cancer,[80,81] and a further study of this combination with the addition of G-CSF.[84] In all 3 studies, irinotecan was given on days 1, 8 and 15, and cisplatin was given on day 1 of every 4-week cycle. In the regimen where G-CSF was added, it was given from days 4 to 21 of each treatment cycle, except on the days of irinotecan administration. In the 2 studies performed without G-CSF, the recommended phase II doses of irinotecan/cisplatin were: 60/80 and 80/60 mg/m^2, respectively. Diarrhoea was dose-limiting in both trials, while neutropenia was also dose-limiting in one of these trials but moderate in the other. The addition of G-CSF allowed escalated doses of 80 mg/m^2 to be safely administered together for both agents, and the dose-limiting toxicity seen was diarrhoea. No pulmonary toxicity was observed in any of these trials. Overall response rates were in the range of 33 to 54% among patients with NSCLC and 100% in 2 patients with SCLC in 1 study.[81] A complete response was observed in one of the studies that was conducted without G-CSF,[81] but the responder's histological type of lung cancer was not specified.

Mori et al.[85] performed a phase I study in patients with NSCLC to establish the optimum doses for combination therapy with cisplatin given as an infusion continuously from days 1 to 5 and irinotecan given as a 90-minute infusion on day 1, repeated every 4 weeks. Neutropenia was dose-limiting in this regimen and 1 patient developed severe pneumonia and sepsis associated with grade 4 neutropenia. The recommended phase II doses were 20 mg/m^2/day for cisplatin and 80 mg/m^2 on day 1 for irinotecan. Although no patients had a complete response, partial responses were achieved in 9 of 19 assessable patients (47%).

Shinkai et al.[86] reported 2 successive phase I trials evaluating the feasibility of combining irinotecan, cisplatin and vindesine in the treatment of NSCLC, without growth factor support. Irinotecan and vindesine were given on days 1 and 8, while cisplatin was given only on day 1, in 3- to 4-week cycles. The recommended phase II dose of irinotecan was 37.5 mg/m^2 on days 1 and 8 when combined with vindesine (3 mg/m^2) and high-dose (100 mg/m^2) cisplatin, while the recommended phase II dose of irinotecan was 80 mg/m^2 on days 1 and 8 when combined with vindesine (3 mg/m^2) and low-dose cisplatin (60 mg/m^2). Diarrhoea and neutropenia were dose-limiting in both trials. No pulmonary toxicity related to drug administration was recorded. Three of 46 patients had a grade 3 elevation of transaminase levels. Partial responses were seen in 15 of 33 (45%) assessable patients. Again, no complete responses were observed.

Shirao et al.[87] conducted a phase I-II study of irinotecan combined with fixed-dose cisplatin in 24 patients with advanced gastric cancer. Irinotecan was administered as a 90-minute infusion on day 1, followed 2 hours later by a 120-minute infusion of cisplatin 80 mg/m^2. Irinotecan alone at the same dose was administered again on day 15, and the treatment was repeated every 4 weeks. The dose-limiting toxicity observed was neutropenia. Grade 3 or 4 diarrhoea occurred in 3 of 24 patients (13%). The recommended doses and schedule were irinotecan 70 mg/m^2 on days 1 and 15, and cisplatin 80 mg/m^2 on day 1. There were no complete responders in this study, although 10 of 24 patients (42%) did show partial responses. Among 4 patients who were chemotherapy-naive, 3 (75%) responded to therapy.

4.2 Phase II Trials

The results of phase II trials of irinotecan given in combination with other cytotoxic agents are summarised in table V. Most of these studies are ongoing and so only preliminary data are currently available.

In 2 trials involving patients with metastatic colorectal cancer, combination therapy with irino-

tecan and fluorouracil/calcium folinate was administered on alternating cycles to previously untreated patients. In the study by Rothenberg et al.,[88] irinotecan was given on the commonly utilised US schedule of weekly for 4 weeks over a 6-week cycle, but at a slightly lowered dose of 100 mg/m^2. In the study by Barone et al.,[89] irinotecan was administered at the standard European dosage and schedule of 350 mg/m^2 every 3 weeks. In both studies, after the initial treatment cycle of irinotecan, fluorouracil 425 mg/m^2 and calcium folinate 20 mg/m^2 were given on days 1 to 5 in a 4-week cycle, followed by alternate administration of the 2 regimens.

Response rates of 26 and 21% were reported by the US and European studies, respectively. These results are somewhat disappointing since they are not superior to those achieved with either irinotecan or fluorouracil/calcium folinate alone in this patient population.[48,50,51,98] In the US study, grade 3 and 4 diarrhoea were observed in 15.7% of patients receiving irinotecan and in 4.6% of patients receiving 5 fluorouracil/calcium folinate. Other toxicities, including myelosuppression, were mild and were similar to those observed with either therapy given alone. In the European study, neutropenia and diarrhoea were the most common adverse effects noted on preliminary analysis. Longer term follow-up and details on cumulative toxicity would be useful to determine if there are therapeutic advantages to these protocols.

Three phase II trials[90-92] of irinotecan given in combination with either cisplatin or etoposide to patients with NSCLC have been performed by adopting the recommended doses from prior phase I trials. In one of these studies,[92] G-CSF was added to permit a higher than previously recommended dose of irinotecan to be co-administered with infusional cisplatin. The overall response rates in these 3 studies ranged from 21 to 54%, which are comparable to those obtained with other conventional combination regimens in NSCLC. In one of these studies,[91] complete response was reported in 2 of the 52 evaluable patients treated with irinotecan plus cisplatin. Among the 154 patients entered on these 3 trials, grade 3 to 4 diarrhoea occurred in 16 to 25% and grade 3 to 4 leucopenia in 13 to 23%. In the study by Oshita et al.,[90] concurrent administration of irinotecan and etoposide for 3 consecutive days every 3 weeks with G-CSF support resulted in interstitial pneumonitis in 3 of 61 patients (5%). These episodes of pneumonitis were associated with hypoxemia and a diffuse reticular shadow on chest x-ray, all of which improved with corticosteroid treatment.

In a phase II study conducted in Japan,[93] irinotecan was administered concurrently with thoracic irradiation to 24 patients with previously untreated, unresectable stage IIIA/B NSCLC. 17 patients (71%) completed all 6 courses of irinotecan and 21 patients (88%) completed 60Gy radiation treatment as planned. Although no complete responses were obtained, partial responses were seen in 19 patients (79%), suggesting that this regimen is highly active in locally advanced NSCLC. Three patients developed grade 3 hypoxemia caused by pneumonitis, which may have been related to irinotecan, radiation or an interaction of the 2 therapies. Pulmonary toxicity was the most prominent toxicity associated with this regimen so far. Other toxicities reported were neutropenia, esophagitis and fever.

A phase II study combining irinotecan and cisplatin in previously untreated SCLC was recently reported.[94] Among 40 patients with limited disease, there were 12 complete and 21 partial responders for an overall response rate of 83%. The overall response rate among 35 patients with extensive disease was 86%, with complete and partial responses achieved in 10 and 20 patients, respectively. Haematological toxicity especially in the form of neutropenia and leukopenia were commonly observed. Grade 3 and 4 diarrhoea occurred in 19% of patients, and 2 patients died with concomitant diarrhoea and myelosuppression. No pulmonary toxicity was noted during chemotherapy. Thoracic irradiation was delivered to responders with limited disease after 4 cycles of chemotherapy and prophylactic cranial irradiation was offered to those who attained a complete response. Interest-

ingly, 4 patients whose disease did not respond to irinotecan plus cisplatin subsequently received cyclophosphamide, doxorubicin and etoposide, but the SCLC did not respond to this second line treatment in any of the patients. Ten patients whose cancer relapsed after initial response to irinotecan plus cisplatin, were offered the same salvage regimen, 1 patient achieved a complete response and 4 achieved partial responses.

In ovarian cancer, both the adenocarcinoma and clear cell histological subtypes have shown good responses to irinotecan-based regimens.[95,96] Overall response rates of 55 to 60% have been observed using irinotecan either in combination with intravenous cisplatin,[95] or with intraperitoneal mitomycin C.[96] Complete response rates of 18% (2 of 11 patients) and 40% (8 of 20 patients), respectively, were obtained with these regimens.

Promising phase II results were also noted using an irinotecan and cisplatin combination therapy in patients with gastric cancer,[97] with an overall response rate of 48%, including 1 complete response, and a median survival of 10.2 months among a mixture of previously treated and untreated patients. A response rate of 59% was obtained in the subgroup of 29 chemotherapy-naive patients.

In light of these encouraging results, comparison of irinotecan-based regimens with conventional therapy are warranted in these types of malignancy.

5. Risks of Irinotecan Therapy

5.1 Gastrointestinal Toxicity

5.1.1 Cholinergic-Like Syndrome

Irinotecan can produce an early cholinergic-like syndrome that typically occurs acutely during or immediately after its infusion.[39,99-101] At lower doses (100 to 260 mg/m^2), the most common signs and symptoms of this syndrome are abdominal cramps, early diarrhoea and diaphoresis. At higher doses (300 to 750 mg/m^2), patients may, in addition, experience visual accommodation disturbances, lacrimation and salivation. The incidence of this reaction is variable, but in a French study of 213 patients who received irinotecan at 350 mg/m^2 every 3 weeks as a 30-minute infusion, up to 85% of patients developed symptoms of varying degrees.[50,100]

These adverse events usually subside spontaneously within 1 to 2 hours, but prompt resolution can be obtained with atropine (e.g. 0.5 to 1mg subcutaneously or intravenously), especially when the predominant adverse effect is painful abdominal cramps. Treatment with diphenhydramine has also been effective in providing symptomatic relief. Prolongation of the infusion duration may be helpful, but extension beyond 90 minutes is not recommended. A premedication regimen consisting of ondansetron and diphenhydramine can also reduce or prevent these acute toxicities.[38]

This cholinergic-like syndrome may be related to the piperidino side chain of irinotecan, which has structural similarities to dimethylphenylpiperazinium,[102] a highly selective and potent stimulator of nicotinic receptors in the autonomic ganglion. The inhibition of cholinesterases by irinotecan is not a likely mechanism for these effects, since serum cholinesterase activity did not show any significant differences when measured pre- and post-treatment with irinotecan.[99]

5.1.2 Delayed-Onset Diarrhoea

A second pathophysiologically distinct type of diarrhoea has been identified as being associated with irinotecan therapy. In contrast to the early-onset diarrhoea which is seen as part of the acute cholinergic-like syndrome, the onset is delayed. On the once every 3 weeks schedule, the median time to onset of the first delayed diarrhoeal episode is 5 to 6 days after drug administration.[50,103] On the weekly for 4 weeks over a 6-week cycle schedule, the median time to onset is 10 days (i.e. 3 days following the second weekly dose of irinotecan).[42]

Delayed-onset diarrhoea tends to be more severe and protracted compared with the early-onset type, and generally requires pharmacological and supportive measures in its management. An effective antidiarrhoeal regimen developed by Abigerges et al.[103] to abrogate this toxicity has been widely adopted, with occasional minor mod-

ifications. Loperamide 2 to 4mg orally is to be taken at the first sign of diarrhoea, followed by 2mg orally every 2 hours (4mg orally every 4 hours at night) until there is complete resolution of diarrhoea for at least 12 hours. If, at the end of 3 consecutive days of continuous loperamide therapy, the diarrhoea is not controlled and/or the patient becomes dehydrated, hospitalisation for intravenous fluid replacement is recommended. The early initiation and vigilant compliance with this intensive loperamide therapy have reduced the incidence of delayed-onset diarrhoea to acceptable levels.

The prophylactic use of acetorphan, an orally administered enkephalinase inhibitor, is being investigated as a potential preventive treatment for delayed-onset diarrhoea induced by irinotecan.[104] However, preliminary results have been disappointing: acetorphan given as a preventive measure did not decrease the incidence or the duration of delayed-onset diarrhoea.[105]

The mechanism of irinotecan-related delayed-onset diarrhoea is not well understood, but appears to stem from a secretory process, with an exudative component.[106] Ikuno et al.[107] examined the mucosal changes in the intestines of mice 6 days after the first dose of intraperitoneal irinotecan administration, which included epithelial vacuolation and apoptosis in the ileum, and goblet-cell hyperplasia with excessive amount of mucin in the caecum.

Correlations between irinotecan pharmacokinetic parameters and the severity of diarrhoea have been inconsistent. Some investigators reported a significant linear correlation between diarrhoea grade and the AUC of irinotecan and/or SN-38,[108-110] while no relationship was detected by others.[38]

Gupta et al.[111] calculated a biliary index to assess the relationship between gastrointestinal toxicity and the pharmacokinetics of irinotecan and its metabolites. The active primary metabolite of irinotecan, SN-38, has been shown to undergo glucuronic acid conjugation to form the corresponding glucuronide (SN-38G), which is present in significant concentrations in plasma, bile and urine.[112-114] SN-38G is then deconjugated by the intestinal microflora to regenerate SN-38,[18] and accumulation of SN-38 in the intestine has been linked to irinotecan-induced diarrhoea in nude mice.[115] The biliary index estimates the exposure of SN-38 in the bile, and is defined as the product of the AUC values of irinotecan and SN-38 divided by that of SN-38G. Patients with grade 3 and 4 diarrhoea have been shown to produce higher index values as compared with those with grade 0 to 2 diarrhoea.[111] Abnormalities in glucuronidation may be associated with an increased risk of gastrointestinal toxicity from irinotecan therapy. Patients who have decreased glucuronidation, such as those with Gilbert's syndrome, appear to have enhanced biliary excretion of unconjugated SN-38 and may thus be more susceptible to irinotecan-induced diarrhoea.[116]

5.1.3 Other Gastrointestinal Effects

Other gastrointestinal adverse effects associated with irinotecan administration include nausea and vomiting, which are generally manageable with anti-emetic therapy. Grade 3 and 4 toxicity occurs in about 15 to 20% of patients.

Rothenberg et al.[42] described the development of akathisia in 2 patients who received prochlorperazine as an anti-emetic before administration of irinotecan. The absence of this symptom complex with either drug administered alone in these patients suggests a possible drug interaction.

5.2 Haematological Toxicity

Besides diarrhoea, myelosuppression in the form of leucopenia/neutropenia, has been identified as the other principal dose-limiting toxicity of irinotecan therapy. On the once every 3 weeks schedule, neutrophil nadir occurs early at around days 6 to 9,[39,50] whereas on the weekly for 4 weeks over a 6-week cycle, neutrophil nadir occurs later at around day 15.[42] The duration of neutropenia is usually short-lived (<5 days), asymptomatic and noncumulative on both schedules. However, sepsis and fatal infectious complications have been reported,[50] especially when severe diarrhoea and neutropenia occur concomitantly.

Other haematological toxicities, thrombocytopenia and anaemia, are generally mild to moderate and do not require therapeutic interventions.

5.3 Other Toxicities

Other toxicities of irinotecan therapy include asthenia, alopecia, pulmonary toxicity and elevation of hepatic transaminase levels.

Fatigue or asthenia occurs in 76 to 80% of patients, and can be severe in 12 to 20%, although in many cases this symptom may be attributed to the underlying disease rather than to the drug.[117] Alopecia, usually partial, occurs in about 60 to 81% of patients receiving irinotecan.[117]

Sporadic cases of interstitial pneumonitis have been reported, and appear to be more prevalent among patients with primary lung cancers.[56,58] The mechanism of this pulmonary toxicity is unknown and may represent an idiosyncratic reaction. Among the 8 patients who developed interstitial pneumonitis in 2 phase II lung cancer studies of irinotecan,[56,58] most had clinical manifestations of dyspnea and fever. One study[58] noted that the interval from the beginning of irinotecan administration to the onset of pulmonary symptoms ranged from 42 to 175 days, with a median of 61 days. Seven of the patients had a diffuse reticulonodular pattern on chest x-ray and the remaining patient showed an abnormality highly suggestive of interstitial infiltrates found only by chest computed tomography. Corticosteroids were given to 7 of the patients, and among them 5 improved with therapy and 2 died from respiratory failure. In 1 patient, toxicity resolved spontaneously and did not require the initiation of corticosteroid treatment.

A transbronchial biopsy was performed prior to corticosteroid therapy in 1 patient who subsequently died as a result of progressive respiratory insufficiency. Pathological examination revealed interstitial oedema associated with fibroblastic proliferation and lymphoid cell infiltration. Fibrinous exudate formed hyaline-like membranes in several air spaces. Most of the alveolar-lining pneumocytes were enlarged and atypically reacted. These findings were compatible with drug-induced changes.

6. Conclusions

Irinotecan possesses an impressive spectrum of antitumour activity against several tumour types, including colorectal, lung, ovarian, cervical and gastric cancers and non-Hodgkin's lymphoma. It is the first drug developed since fluorouracil to have consistent activity in patients with metastatic colorectal cancer.

Phase I studies performed to date have provided useful information on optimal administration and scheduling of irinotecan, as well as thorough evaluation of its adverse effects. Phase II trials using either irinotecan alone or in innovative combinations with other cytotoxic agents are actively ongoing. Further development of this agent will proceed with trials to compare promising irinotecan-based regimens with conventional therapies, and to explore its efficacy when combined with cytostatic agents. Investigations of an oral formulation of irinotecan are being initiated.

As clinical experience with irinotecan accumulates, its toxicity profile will be more clearly elucidated and more effectively modified. This will undoubtedly improve the therapeutic index and allow safer delivery of irinotecan in future studies.

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