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Clinical advances with topoisomerase I inhibitors in gastrointestinal malignancies

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Phase III studies have shown irinotecan prolongs survival significantly when compared with either best supportive care or best infusional 5-fluorouracil (5-FU)-based chemotherapy in patients with 5-FU-resistant colorectal cancer. Phase I/II studies are investigating the combination of irinotecan with 5-FU, with thymidylate synthase inhibitors, notably raltitrexed, and with the oral fluoropyrimidines. Preliminary results suggest irinotecan and raltitrexed can safely be combined in the clinic and that this combination is active. The combination of irinotecan with the oral fluoropyrimidines also has produced promising results. A phase I study of irinotecan plus 5-FU/folinic acid showed high activity in first-line metastatic disease and further trials using the doses of 80 mg/m² irinotecan plus 2 g 5-FU weekly are recommended. The combination of irinotecan with the De Gramont 5-FU regimen is feasible and active in patients with 5-FU-resistant metastatic disease. Alternating exposure to irinotecan and 5-FU may be as active as either treatment alone, and has been associated with overall response rates (ORRs) greater than 30% and encouraging median survival. The combination of irinotecan with oxaliplatin is also feasible and levels of response rates are in the region of 50% (especially with a 2-weekly administration schedule). In patients with advanced gastric cancer (including those with pretreated disease) ORRs of around 50% have been reported following administration of either cisplatin plus irinotecan or cisplatin plus docetaxel. [© 1999 Lippincott Williams & Wilkins.]

Key words: 5-Fluorouracil, colorectal cancer, docetaxel irinotecan, oxaliplatin, ralititrexed.

Introduction

The topoisomerase I inhibitors represent an interesting and potentially important new family of agents. Its members include not only topotecan (9-dimethylaminomethyl-10-hydroxycamptothecin; Hycamtin) and irinotecan (CPT-11) but also the currently less well-developed drugs 9-aminocamptothecin (9AC) and 9-nitrocamptothecin (9NC). Nevertheless, not all agents in this class have substantial activity against gastrointestinal (GI) tumors.

Whilst topotecan is active in ovarian and small cell lung cancer, its activity in metastatic colorectal cancer is modest.[1,2] Using a regimen of 1.5 mg/m² administered as a 30 min i.v. infusion on days 1–5 every 3 weeks, Creemers *et al.* treated a total of 57 evaluable patients, reporting an overall response rate (ORR) of only 7% (95% CI 2–17%).[1] Grade 3–4 neutropenia was observed in 79% of patients. Using a different regimen, of continuous i.v. infusion of 0.5 mg/m² topotecan for 21 days administered every 4 weeks, one complete response was reported in 41 evaluable patients, with an ORR of 10% (95% CI 3–23%) and a 20% incidence of neutropenia.[2] There have been two further studies of the short i.v. infusion regimen in GI cancer. Benedetti *et al.* reported an ORR of 10% in 20 evaluable patients, accompanied by a 50% incidence of neutropenia.[3] Saltz *et al.* found an ORR of 0% among 13 patients.[4]

9AC has shown modest activity in non-small cell lung cancer but appears to be ineffective against metastatic colorectal cancer.[5] 9NC, from the outset, was developed in an oral formulation.[6] 9NC has shown promising activity in pancreatic cancer, with an ORR of 32% reported, trials are

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Table 1. Toxicity and survival in two randomized phase III trials of irinotecan versus best supportive care (BSC) and infusional 5-fluorouracil (5-FU)-based chemotherapy[13,14]

	V301		V302	
	Irinotecan (%)	BSC (%)	Irinotecan (%)	5-FU (%)
No. of patients	*n*=189	*n*=90	*n*=127	*n*=129
Grade 3/4 toxicities				
neutropenia	22	–	14	2
+ fever/infection	3	–	6	2
diarrhea	22	6	22	11
vomiting	14	8	14	5
asthenia	15	19	13	12
mucositis	2	1	2	5
Survival (months)				
6	72	54	78	65
9	53	29	63	47
12	36	14	45	32

awaited to provide data on its activity in colorectal cancer.[7]

In colorectal cancer, irinotecan has shown interesting activity. Phase II studies provided confirmation of efficacy in the second-line setting for two regimens: 100–125 mg/m^2 per week administered for 4 of 6 weeks (US studies) and 350 mg/m^2 administered once every 3 weeks (European studies).[8–12] With each regimen, an ORR of 13% was observed in a total of 759 patients studied. Stable disease was seen in 40–50% of patients, with progression-free survival of 4 months and survival duration of 9 months. GI side-effects were the dose-limiting toxicities (DLTs).

To evaluate the effect of irinotecan on survival and quality of life, and to compare the benefit–risk ratio of this treatment with that of alternatives, two phase III trials were undertaken in the setting of second-line colorectal cancer.[13,14] In one trial (V301), a total of 279 patients were randomized in a ratio of 2:1 to either the irinotecan arm (350 mg/m^2 as a 90 min infusion once every 3 weeks) plus best supportive care (BSC) or to BSC alone.[13] In a second study (V302), the same schedule of irinotecan was compared to the best estimated infusional 5-fluorouracil (5-FU)-based regimen (two out of three regimens prospectively selected by each center).[14]

Patients assigned to irinotecan were 2.6 times more likely to survive to 1 year than patients assigned to BSC alone (Table 1). Compared with best 5-FU-based regimen, patients randomized to irinotecan were 1.4 times more likely to survive 1 year.

The findings from these two phase III studies supported the activity observed with irinotecan in the phase II studies. The implications of these results are important in that irinotecan may be considered a new standard of care in colorectal cancer patients who have failed 5-FU.

Irinotecan in combination with raltitrexed or oral fluoropyrimidines

Based on the single-agent activity, irinotecan is now being studied in combination with several other agents. Raltitrexed (Tomudex) is a novel and specific inhibitor of thymidylate synthase (TS) with an ORR of 19–26% (activity comparable with that of 5-FU$_{bolus}$/folinic acid) in first-line metastatic colorectal cancer.[15–17] The principal toxicities of raltitrexed are diarrhea, leukopenia and increased transaminases, which are usually short lived. Irinotecan and raltitrexed have entirely different mechanisms of action and several *in vitro* models have suggested potential clinical synergy between them. Their combination is therefore being evaluated in phase I/II studies involving colorectal cancer patients requiring first-line chemotherapy.

Based on experience in laboratory models, the schedule chosen for investigation was irinotecan administered as a 30 min infusion followed after an interval of 1 h by raltitrexed as a 15 min infusion, every 3 weeks. Doses have been escalated from 175 mg/m^2 irinotecan plus 2.6 mg/m^2 raltitrexed to 350 mg/m^2 irinotecan plus 3 mg/m^2 raltitrexed, which is the maximum tolerated. Lethargy was the DLT.

Table 2. Phase I study of irinotecan combined with AIO regimen: dose-escalation design and incidence of DLT[22]

Dose level	Schedule (weeks)	Irinotecan (mg/m^2/day) weekly	Leucovorin (mg/m^2/day) weekly	FU (mg/m^2/day) weekly	No. of patients entered	DLT
1	4	80	500	1.8	3	NO
2	4	80	500	2.0	3	NO
3	4	80	500	2.3	4	NO
4	4	80	500	2.6	3	NO
5	6	80	500	2.3	3	NO
6	6	80	500	2.6	3	NO
7	6	100	500	2.6	6	reached

AIO regimen, see text for details; DLT, dose-limiting toxicity; FU, fluorouracil; NO, not observed.

Rather than the expected diarrhea, mild constipation was reported in the majority of patients. Activity was seen, with partial response or stable disease occurring at most dose levels. An expanded phase II study is underway.

There is also potential for the combination of irinotecan with the oral fluoropyrimidines UFT and capecitabine, both of which are active in colorectal cancer.

UFT is a 5-FU pro-drug which also contains uracil. Uracil inhibits dihydropyrimidine dehydrogenase, which metabolizes 5-FU, leading to a sustained increase in its level.[18] UFT is administered together with folinic acid to provide continuous exposure of reduced folates and so maximize TS inhibition. Activity in advanced and metastatic colorectal cancer has been observed with UFT in phase II studies.[19,20]

A phase I study, where UFT plus folinic acid administered for 14 days in combination with irinotecan on day 1, every 21 days, is ongoing. The dose-escalation design calls for a stepwise increase from 250 mg/m^2 UFT/15 mg/m^2 folinic acid plus 250 mg/m^2 irinotecan to 300 mg/m^2 UFT/15 mg/m^2 folinic acid in combination with 350 mg/m^2 irinotecan.

Capecitabine is also an oral 5-FU pro-drug, which are tumor-selective fluoropyrimidine agents. Preclinical studies demonstrated activity in colorectal, breast, and head and neck carcinomas, including those resistant to 5-FU. An ORR of 24% has been reported in first-line metastatic colorectal cancer, with the main toxicities diarrhea, nausea and vomiting.[21] In a planned phase I/II study, irinotecan 70 mg/m^2 administered weekly for 6 weeks will be combined with capecitabine 2000–2500 mg/m^2 administered on days 1–14 and 22–36.

Irinotecan/5-FU combinations

Both irinotecan and infusional 5-FU/folinic acid regimens have significant single-agent activity in metastatic colorectal cancer. These agents have different mechanisms of cytotoxicity, and *in vitro* and *in vivo* works have suggested schedule-dependent synergistic antitumor activity. Investigation of their combined use in the clinic was therefore a logical step.

In a multicenter phase I study conducted in Germany, 26 colorectal cancer patients who had not previously been treated for metastatic disease received the irinotecan/5-FU combination.[22] Irinotecan was administered as a 90 min i.v. infusion according to a protocol which allowed dose escalation from 80 to 160 mg/m^2 together with an increasing 5-FU dose, from 1.8 to 2.6 g/m^2, administered as a 24 h continuous infusion and folinic acid 500 mg/m^2 as a 2 h infusion (the AIO regimen). Treatment was repeated weekly for 4–6 weeks, followed by a 1 week break. DLT (diarrhea, vomiting and neutropenia) was reached at the dose of 100 mg/m^2 irinotecan plus 2.6 g/m^2 5-FU administered for 6 weeks (Table 2). Of the 26 patients (median age 60 years), 16 had liver metastases and 10 had lung lesions. Of 25 evaluable patients, 16 showed an objective response (ORR 64%, 95% CI 45–83%) and the remainder had minor responses or stable disease. This level of activity was high. The recommended regimen for further study is 80 mg/m^2 irinotecan plus 2.6g/m^2 5-FU and 500 mg/m^2 folinic acid administered weekly for 6 weeks followed by 1 week of rest. However, based on further experience with this regimen the recommended dose of 5-FU is now 2.0 g/m^2 because of a relatively high percentage of diarrhea.

Irinotecan has also been combined in a French phase I study with the 'De Gramont regimen' of infusional 5-FU.[23,24] Fifty-five patients with metastatic colorectal cancer who had failed 5-FU therapy received irinotecan on day 1 as a 90 min i.v. infusion followed after 1 h by 200 mg/m^2 folinic acid as a 2 h infusion and 5-FU 400 mg/m^2 as an i.v. bolus, followed by 5-FU 600 mg/m^2 as a continuous infusion over 22 h. On day 2, the folinic acid infusion and the 5-FU (De Gramont regimen: 200 mg/m^2 folinic acid as a 2 h infusion and 5-FU 400 mg/m^2 as an i.v. bolus, followed by 5-FU 600 mg/m^2 as a continuous infusion over 22 h) was administered. Treatment was repeated every 2 weeks. In this study, the dose of irinotecan was raised in stages from 100 to 300 mg/m^2. Of the 55 patients (median age 59 years), 45 had liver metastases and 29 lung lesions. The median number of previous lines of chemotherapy was 2 (range 1–5). In this heavily pretreated population, antitumor activity was seen at all dose levels.[23–25] In 35 evaluable patients, one complete response and seven partial responses were observed (ORR 23%). Minor responses were seen in six and disease stabilization in 16 patients. The recommended dose for further studies in combination with the De Gramont regimen is 180 mg/m^2 irinotecan.

Further studies have investigated regimens in which irinotecan is alternated with 5-FU/folinic acid in the first-line treatment of metastatic colorectal cancer. In a study from Leuven, 350 mg/m^2 irinotecan was administered on day 1 followed 3 weeks later by the Mayo clinic regimen (bolus 5-FU 425 mg/m^2 plus 20 mg/m^2 folinic acid × 5 days), with irinotecan delivered again after a further 3 weeks.[26] Researchers in the US have used a similar approach, with irinotecan 100 mg/m^2 administered weekly for 4 weeks followed after a 2 week break by the Mayo clinic regimen.[27] In the Leuven trial, an overall response of 30% (95% CI 16–49%) was observed in 33 evaluable patients, with a median time to progression of 7.2 months and median survival of 16 months. In the US trial, the overall response in 71 patients was 32% (95% CI 22–43%), with a median time to progression of 6.9 months and median survival of 17.8 months.

A European phase III study in first-line colorectal cancer has compared high-dose infusional 5-FU (either the De Gramont or AIO regimens, at the investigators' discretion; group B) with high-dose infusional 5-FU plus irinotecan (group A). Three-hundred and eighty-seven patients were randomized into the trial.[28] Over two-thirds of patients had received the De Gramont schedule. The primary endpoint was progression-free survival. Patient characteristics for groups A and B, respectively, included: median age, 62 versus 59 years; perfomance status = 0, 49 versus 51%; prior adjuvant chemotherapy, 26 versus 24%; ≥2 organs involved, 41 versus 36%. A progression free survival of 35.1 weeks versus 18.6 weeks and a response rate of 39 versus 22% was observed for groups A and B, respectively. The safety profile of this combination was tolerable and manageable. An EORTC trial of the AIO regimen alone versus the AIO regimen plus weekly irinotecan is ongoing.

Irinotecan plus oxaliplatin

While irinotecan and its active metabolite SN38 inhibit topoisomerase I activity and stabilize the cleavable complex, oxaliplatin (a DACH platin) is cytotoxic because of the formation of DNA intra- and inter-strand cross-links.[29] Activity has been observed with oxaliplatin is the treatment of colorectal cancer.[30,31] The possibility of synergy with irinotecan is suggested by the fact that SN38 slows the reversal of oxaliplatin-induced cross-links, while oxaliplatin increases the cytotoxicity of SN38-induced topoisomerase I cleavable complexes. SN38 and oxaliplatin show strong synergy in the HT29 human colon cancer line.[32] The fact that irinotecan and oxaliplatin have non-overlapping toxicities and are not cross-resistant provides further rationale for their combination.

Two phase I studies were conducted in 5-FU pretreated patients who had not been exposed to either irinotecan or oxaliplatin. In the first dose-escalation study, using a 3-weekly schedule, oxaliplatin 85–110 mg/m^2 over 2 h was followed after a 1 h interval by irinotecan 150–250 mg/m^2 administered over 30 min.[33] In the second study, drugs were administered on a 2-weekly schedule at the fixed dose of 85 mg/m^2 oxaliplatin over 2 h followed after 1 h by irinotecan in the dose range 100–200 mg/m^2 administered over 30 min.[34,35]

The patients enrolled in the two studies were demographically representative of patients with advanced colorectal cancer: the median age was 54 years, the majority of patients had a WHO performance status of 0 or 1, almost all patients had received prior chemotherapy and more than half had shown clinical progression while receiving 5-FU (Table 3).

Among the 17 evaluable patients, with 5-FU-resistant colorectal cancer, who received the 3-

Table 3. Patient characteristics of phase I studies of irinotecan and oxaliplatin[33,34]

	Three-weekly schedule[34]	Two-weekly schedule[33]
Patients treated/evaluable	26/26	20/20
Male : female ratio	19 : 7	16 : 4
Median age in years (range)	54 (28–66)	53 (35–76)
WHO performance status		
0	17	8
1	8	7
2	1	5
Patients with previous chemotherapy	24	17
Disease progression while receiving prior 5-FU	13	12

WHO, World Health Organization; FU, fluorouracil

weekly schedule, appreciable activity was observed.[34,35] Partial response was obtained in 41% of patients and stable disease in a further 35% of patients. At the highest dose administered in this phase I study (oxaliplatin 110 mg/m^2 plus irinotecan 250 mg/m^2), grade 3/4 neutropenia occurred in 22% of the nine cycles administered; diarrhea was observed in 11% of cycles, nausea/vomiting in 33% and peripheral neurotoxicity in 11% of the cycles. DLT was observed in five out of seven patients treated. However, after entering additional patients at the immediate lower dose level (oxaliplatin 110 mg/m^2 plus irinotecan 200 mg/m^2), neutropenia occurred in 12% of the 41 cycles administered. Diarrhea occurred in 29% of the 41 cycles, nausea/vomiting in 7% and peripheral neuropathy in 15% of cycles; DLT was observed in five out of 13 patients. Based on these data, the maximum tolerated dose of the combination was considered to be 200 mg/m^2 irinotecan plus oxaliplatin 110 mg/m^2 and the dose recommended for further studies was 200 mg/m^2 irinotecan plus 85 mg/m^2 oxaliplatin. The DLTs were diarrhea and neutropenia. No pharmacokinetic interaction was seen when the two drugs were administered according to the schedule outlined.

In patients who received the combination on the 2-weekly schedule, the DLT was reached at the level of 200 mg/m^2 irinotecan plus 85 mg/m^2 oxaliplatin, at which point grade 4 neutropenia occurred in 41% of cycles.[33,35] In 11 evaluable patients with advanced colorectal cancer, one complete response was observed. Six patients had a partial response (ORR 64%) and the remaining four patients had stable disease with no patients having outright progressive disease.

A further increase in dose density may be possible. Scheithauer *et al.* have investigated a schedule where irinotecan 85 mg/m^2 is administered on days 1, 8 and 15 together with oxaliplatin 85 mg/m^2 on days 1 and 15, every 4 weeks.[36] Among the 36 patients treated (all of whom had failed prior 5-FU therapy), there were two complete responses and 13 partial responses (ORR 42%), and the time to progression was 7.5 months. Grade 3 diarrhea occurred in 19% of patients, grade 3/4 neutropenia in 20% and grade 3 peripheral neuropathy in 8%.

In a phase I study involving metastatic solid tumors, Ychou *et al.* are investigating a triple combination of irinotecan 90–240 mg/m^2 administered on day 1 along with oxaliplatin 60–85 mg/m^2, followed by the De Gramont 5-FU/folinic acid regimen on days 1 and 2 (Tchow, personal communication).

Docetaxel or irinotecan plus platinum in gastric cancer

The past decade has taught us that gastric cancer is a chemosensitive disease, that the optimum means of administering 5-FU is by infusion and that cisplatin may be a valuable agent in combination. More recently, there have been indications that the oral fluoropyrimidines are also active. The present paper, however, is focussed on docetaxel, irinotecan, and the platinums.

Sulkes *et al.* administered docetaxel at the classical dosage of 100 mg/m^2, where a 22% ORR in 37 first-line gastric cancer patients was observed.[37] Docetaxel is also active in second-line gastric cancer, with response rates ranging from of 9 to 24% with varying doses of docetaxel (60–100 mg/m^2) in patients with disease resistant to 5-FU- or cisplatin-based chemotherapy.[38–40]

Docetaxel and platinum agents have different mechanisms of action; both are active in gastric

cancer, docetaxel is active *in vitro* in platinum-resistant cell lines and docetaxel is active in patients pre-treated with cisplatin. Their use in combination was therefore studied by Roth *et al.*[41] Docetaxel was administered at a dose of 85 mg/m^2 as a 1–2 h infusion followed by a 75 mg/m^2 cisplatin infusion over 4 h, every 3 weeks. Forty-eight patients with bidimensionally measurable metastatic or locally advanced gastric cancer who had not previously received chemotherapy (except possibly in the neoadjuvant setting) were enrolled in this study. A complete response was observed in two patients (4%), a partial response in 25 (52%) and stable disease in a further 12 (25%). The ORR of 56% (95% CI 41–71%) must be regarded as very promising. The median time to progression was 6.6 months and median survival 9 months. Following these encouraging results, a trial is being undertaken in which 450–600 patients with first-line advanced gastric cancer are randomized to receive docetaxel plus cisplatin, docetaxel plus a continuous 5-day infusion of 5-FU plus cisplatin or cisplatin plus 5-FU alone. The primary endpoints of the study are time to progression and quality of life.

Irinotecan is active in gastric cancer when used as a single agent: Futatsuki reported on ORR of 23% in 60 patients and Köhne *et al.* have found a 19% ORR in 32 patients.[42,43] Following this experience, 24 patients (four previously untreated, 20 pre-treated with 5-FU, cisplatin or both) received irinotecan 70 mg/m^2 on days 1 and 15 plus 80 mg/m^2 cisplatin on day 1, every 4 weeks.[44] Three of four untreated patients and seven of 20 pretreated patients showed an objective response, giving an ORR of 42% (95% CI 22–61%). The DLT was neutropenia.

A very similar combination regimen (70 mg/m^2 irinotecan on days 1 and 15, plus cisplatin 80 mg/m^2 on day 1, every 4–6 weeks) has been assessed in 44 evaluable patients.[45] Among the 29 patients with no prior chemotherapy, an ORR of 59% (95% CI 42–74%) was noted. Among 15 pretreated patients, the ORR was 27% (CI 10–52%). The toxicity in this study was manageable. Although grade 4 neutropenia occurred in 57% of cases, neutropenic fever developed in only 5%. Grade 3/4 nausea or diarrhea was experienced by 19–21%. In a current phase II/III trial, 64 patients will be randomized to irinotecan plus cisplatin or to cisplatin plus the AIO regimen of 5-FU/folinic acid. The best of these regimens will then be compared with a reference arm of cisplatin plus 5-day infusional 5-FU.

Discussion

Two phase III studies have demonstrated that second-line colorectal cancer patients treated with irinotecan experience a significant survival advantage when compared with either BSC or best-estimated infusional 5-FU-based chemotherapy. The GI toxicity associated with irinotecan in these trials, notably diarrhea and vomiting, was less than in the phase II studies, suggesting that increased knowledge about how to handle this drug has resulted in improved management of its side-effects. Irinotecan can be considered the new standard of care for colorectal cancer patients who have failed 5-FU and should be the reference arm in studies of investigational new drugs in second-line CRC.

A range of combinations involving irinotecan show considerable promise. Among them, the administration of irinotecan with 5-FU/folinic acid (administered either concurrently or in alternating schedules) has been extensively studied. These combinations show clear indications of activity and lower than expected toxicity; this has recently been confirmed by a large randomized phase III study.

Preliminary data on the combination of irinotecan with oxaliplatin also appear extremely promising, especially when the drugs are administered every 2 weeks. The dose recommended for further study is irinotecan 200 mg/m^2 plus oxaliplatin 85 mg/m^2. Interestingly, this is the same as the recommendation for the 3-weekly schedule, suggesting that increased dose density has been obtained at no significant cost in increased toxicity: the adverse effects are seen early in the dosing interval and have already resolved by day 15.

In advanced gastric cancer, the activity of cisplatin in combination with either irinotecan or docetaxel is sufficiently encouraging to prompt plans for the neoadjuvant use of such regimens in efforts to increase the efficacy of early treatment of the disease. Although cisplatin is still widely regarded as having an important role in gastric cancer, it would also be appropriate to evaluate the efficacy of docetaxel and irinotecan in combination.

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