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Irinotecan for the treatment of gastric cancer

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Abstract

First-line therapy for metastatic gastric cancer has progressed from the use of 5-fluorouracil (5-FU) in the late 1960s through to an array of combination therapies such as cisplatin/5-FU, FAM (5-FU, doxorubicin, mitomycin), FAMTX (substituting methotrexate for mitomycin) and more recently ECF (epirubicin, cisplatin, 5-FU). Systemic chemotherapy has been shown to prolong survival compared with best supportive care alone, but the median survival for patients is still in the region of 9 months. This is because although gastric cancer is a chemosensitive disease with over 40% of patients showing a response, these responses are of short duration. Furthermore, it is difficult to consider one of the many frequently used regimens as a generally accepted standard for the treatment of these patients. Irinotecan (Campto®, CPT-11) is one of a group of new drugs showing activity in the treatment of gastric cancer, which include docetaxel, paclitaxel, oral fluoropyrimidines and oxaliplatin. Many phase II studies of irinotecan alone or in combination with cisplatin and/or 5-FU showed promising efficacy for the first and second line treatment. Eagerly awaited results of randomised phase III studies with irinotecan are expected to set new standards in the treatment of metastatic gastric cancer.

Keywords: CPT-11; Cisplatin; First-line; Gastric cancer; Irinotecan

1. Introduction

Combination chemotherapy has been shown to offer a modest advantage in the treatment of advanced gastric cancer. Regimens such as cisplatin (CDDP)/5-fluorouracil (5-FU), FAM (5-FU, doxorubicin, mitomycin), FAMTX (substituting methotrexate (MTX) for mitomycin), ELF (etoposide/5-FU/folinic acid [FA]) and more recently ECF (epirubicin, cisplatin, 5-FU) have produced response rates of between 42% and 58% in phase II trials [1–4]. Considering only the results of phase III trials the overall response rates ranged between 20% and 40%. However, the median survival for these patients is still less than 10 months [4], highlighting the unmet medical need in these patients.

For the most part, the combination regimens tested to date in phase III trials have failed to live up to the promise of the corresponding phase II trials. Irinotecan (Campto®, CPT-11) is one of a group of newer agents showing promising activity in patients with gastric cancer. Irinotecan is known to be effective in the treatment of advanced colorectal cancer [5,6] and has shown single-agent activity in gastric cancer [7,8]. A phase II trial showed irinotecan to be active in combination with cisplatin in the treatment of both chemotherapy-naïve [9,10] and pretreated patients [9,11], and in combination with bolus 5-FU/FA in the treatment of previously untreated patients [12] and in pretreated and chemotherapy-naïve patients [13]. In randomised phase II trials irinotecan has been combined with either the high-dose infusional AIO 5-FU/FA regimen or cisplatin [14] or with the intermittent infusional de Gramont 5-FU/FA regimen [15] first-line, and in both studies the irinotecan arm was selected for further investigation in phase III trials. In another randomised phase II study irinotecan

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Table 1
Summary of irinotecan in the treatment of chemotherapy-naïve gastric cancer patients

Study	Treatment	No. of evaluable patients	Response rate (%)	Median survival (months)
Futatsuki *et al.* [7]	Irinotecan 100 mg/m^2 weekly or 150 mg/m^2 for 2 weeks	60	23.3	NA
Kohne *et al.* [8]	Irinotecan 350 mg/m^2 for 3 weeks	35	20	7.1
Combination studies				
Shirao *et al.* [19]	Irinotecan 70 mg/m^2 day 1, 15 plus CDDP 80 mg/m^2 day 1 for 4 weeks	24	42	NA
Boku *et al.* [9]	Irinotecan 70 mg/m^2 day 1, 15 plus CDDP 80 mg/m^2 day 1 for 4 weeks	29	59	11.5
Ajani *et al.* [10]	Irinotecan 65 mg/m^2 day 1, 15 plus CDDP 30 mg/m^2 day 1 weekly for 4 weeks, followed by 2 week rest	36	53	9
Blanke *et al.* [12]	Irinotecan 125 mg/m^2 plus bolus 5-FU 500 mg/m^2, FA 20 mg/m^2 weekly for 4 weeks	36	22	7.6
Findlay *et al.* [13]	Irinotecan 125 mg/m^2 plus bolus 5-FU 500 mg/m^2, FA 20 mg/m^2 weekly for 4 weeks	62	22.6	6.3
Randomised studies				
Pozzo *et al.* [14]	A: Irinotecan 200 mg/m^2 plus CDDP 60 mg/m^2 day 1 for 3 weeks	25	28	6.9
	B: Irinotecan 80 mg/m^2 plus 5-FU 2000 mg/m^2, FA 500 mg/m^2 weekly for 6 weeks plus 1 week rest	72	42	10.7
Bouche *et al.* [15]	Irinotecan 180 mg/m^2 day 1 plus 5-FU/FA (de Gramont)	45	40	11.3
Moehler *et al.* [16]	Irinotecan 80 mg/m^2 plus 5-FU/FA (AIO) days 1, 8, 15, 22, 29, 36 for 7 weeks	34	35	NA
Dank *et al.* [21]	Irinotecan 80 mg/m^2 plus 5-FU 2000 mg/m^2, FA 500 mg/m^2 weekly for 6 weeks plus one week rest	NA	NA	NA
Schleucher *et al.* [17]	Irinotecan 80 mg/m^2 plus 5-FU 2000 mg/m^2, FA 500 mg/m^2 plus CDDP 20-50 mg/m^2 biweekly	17	70	NA

5-FU, 5-fluorouracil; FA, folinic acid; CDDP, cisplatin; NA, not applicable.

in combination with AIO 5-FU/FA was shown to be more effective first-line and at least as safe as an ELF regimen [16]. Irinotecan is also being investigated in a phase I/II study in combination with the AIO 5-FU/FA regimen plus biweekly cisplatin [17] and has been shown to be active in combination with 5-FU/FA (de Gramont) second-line in patients with 5-FU/cisplatin-resistant disease [18]. Thus, irinotecan appears to have a significant contribution to make in the treatment of gastric carcinoma (Table 1).

2. Irinotecan alone

Several studies of irinotecan for the treatment of advanced gastric cancer have been conducted (Table 1). An early Japanese study in 88 patients, 60 of which were evaluable for response, in which irinotecan was administered at a dose of either 100 mg/m^2 weekly or 150 mg/m^2 every two weeks, yielded an overall response rate of 23% in previously treated patients [7]. In a phase II European multicentre trial, of irinotecan 350 mg/m^2, administered every three weeks to chemotherapy-naïve patients with metastatic gastric cancer, two complete and five partial responses (PRs) were achieved among 35 evaluable patients [8]. Sixteen patients achieved stable disease and 12 had progressive disease. Overall 66% of patients benefited from tumour growth control. The median time to progression (TTP) was 3.0 months (95% CI: 5.2–9%). The median overall survival was 7.1 months and the probability of being alive at 6 and 9 months was 61% and 32.4%, respectively. Overall, irinotecan was shown to be active and well tolerated in patients with metastatic gastric cancer.

3. Irinotecan in combination chemotherapy (non-randomised phase II studies)

3.1. Irinotecan and cisplatin

The feasibility of combining irinotecan with CDDP was demonstrated in a Japanese phase I/II dose-escalation study [19]. Irinotecan in combination with CDDP has been administered to chemotherapy-naïve gastric cancer patients in two studies [9,10] and to preteated patients in part of one of these studies [9] and in a separate study [11]. In the trial of Boku *et al*. [9], patients were treated with irinotecan (70 mg/m^2) days 1 and 15 and CDDP (80 mg/m^2) on day 1 every four weeks as recommended by Shirao *et al*. [19]. The overall response rate (ORR) was 48% (21 of 44 patients) and the response rate (RR) of the patients who had not received prior chemotherapy was 59% (17/29 patients). The median survival times were almost 10 months and 11.5 months for the previously treated and untreated patients, re-

spectively. In the trial of Ajani *et al*. [10], patients received irinotecan (65 mg/m^2) plus CDDP (30 mg/m^2) both administered day 1 weekly for four weeks, followed by a recovery period of two weeks. The ORR was 58%, including four patients with complete responses (CRs). Thus, irinotecan in combination with CDDP was clearly active, although the trial of Ajani *et al*. [10] suggested that some modification to the doses and schedule might be warranted to improve tolerability in what is after all a poorly patient population.

3.2. Irinotecan and 5-FU/FA

A phase II study of irinotecan in combination with bolus 5-FU/FA showed this combination to be active in the treatment of patients with advanced gastric cancer. The ORR was 22%. There was no obvious difference in RR between patients treated previously in the adjuvant setting (20%) and those that were untreated (23%). The median TTP was 4.4 months, median response duration 3.7 months and median survival for all patients 7.6 months. This response rate was however considered to be disappointing and was in part attributed by the authors to being the result of dose reductions due to unacceptable bolus 5-FU-related toxicity [12]. Another trial, using an identical dose and schedule of administration [13], yielded a similar ORR and a median survival, for all previously untreated patients, of 6.3 months. Thus, irinotecan in combination with bolus 5-FU/FA is active in the treatment of gastric carcinoma patients but modifications to the regimen used in this trial would have to be made to improve tolerability.

3.3. Irinotecan and docetaxel

There is some evidence of additivity between irinotecan and docetaxel, which are both active in gastric cancer. In a phase I study [20] using an every three weeks schedule, some heavily pretreated patients with gastric cancer experienced tumour growth control. Further studies using less toxic regimens are warranted using weekly and two weekly schedules.

3.4. Irinotecan in combination with 5-FU/FA and cisplatin

All the irinotecan combination regimens described above achieved RRs of between 22% and 53% (Table 1). Recently however the irinotecan/AIO 5-FU/FA regimen has been investigated in combination with escalating doses of CDDP. The results so far, for 35 patients (19 evaluable for response), include 14 objective remissions and 2 PRs to yield a RR of over 70% [17]. The worst toxicities, after multiple cycles, were diarrhoea (17%) and neutropenia (29%). These preliminary results show irinotecan in combination with 5-FU/FA and CDDP to be feasible and to be associated with significant efficacy.

4. Irinotecan in combination chemotherapy (randomised studies)

Two randomised phase II studies of irinotecan in combination with infusional 5-FU/FA regimens have resulted in significantly improved survival times [14,15] (Table 1). In a multinational randomised phase II study, previously untreated patients were randomised to receive irinotecan in combination with either CDDP (irinotecan 200 mg/m^2 plus CDDP 60 mg/m^2 day 1 every three weeks) or the AIO 5-FU/FA regimen (irinotecan 80 mg/m^2, FA 500 mg/m^2 and 5-FU 2000 mg/m^{2}weekly for six weeks, followed by one week's rest) [14]. The ORR assessed by independent reviewers was 28% for the irinotecan plus CDDP arm, and 42% for the irinotecan plus 5-FU/FA arm; TTP was 4.5 months and 6.5 months and overall survival was 6.8 months and 10.5 months for the same two arms. On the basis of these results the data monitoring committee selected the irinotecan/5-FU/FA arm as the test arm for the phase III trial that is currently ongoing [21].

The association of irinotecan in combination with the intermittent infusional de Gramont regimen achieved a RR of 40% and a median progression-free survival (PFS) and OS of 6.7 months and 11.3 months, respectively (Table 1), both of which were superior to the values obtained in the 5-FU/FA alone and the CDDP/5-FU/FA arms [15]. The toxicity profile and efficacy of the irinotecan/infusional 5-FU/FA combination were considered to be highly encouraging and will be assessed in a phase III study. In another randomised trial irinotecan in combination with the infusional AIO 5-FU/FA regimen is being compared with the ELF regimen in terms of efficacy and tolerability [16]. A RR of 35% was achieved in 34 evaluable patients after seven weeks versus 17% in 24 evaluable patients in the ELF arm. The tumour growth control rates for the two treatment arms were 76% and 54%, respectively. In addition the irinotecan/5-FU/FA tolerability was at least as good as that for ELF. Thus, these preliminary data suggest that the irinotecan/5-FU/FA (AIO) regimen is more effective than ELF in the treatment of advanced gastric cancer. Following on from the randomised phase II study of Pozzo *et al*. [14], a phase III randomised study has been initiated to compare irinotecan plus the AIO 5-FU/FA regimen with CDDP plus 5-FU alone. To date, in all these studies irinotecan in combination with infusional 5-FU/FA has shown a predictable and manageable safety profile.

5. Conclusion

Clearly effective regimens are being identified for the first-line treatment of gastric cancer, particularly those based on irinotecan and docetaxel (Van Cutsem, this

supplement). Response rates are now reproducibly around 40% with TTPs of 5–6 months and OSs edging above 10 months [14,15]. The final results of the phase III trials are eagerly awaited. Irinotecan is also showing promise in the second-line setting in patients with platinum resistant tumours [18] and may be predicted to play a role in the future in the adjuvant and neoadjuvant treatment settings that are emerging for this disease.

References

1. MacDonald JS, Schein PS, Woolley PV, *et al*. 5-Fluorouracil, doxorubicin, and mitomycin (FAM) combination chemotherapy for advanced gastric cancer. *Ann Intern Med* 1980, **93**, 533–536.
2. Glimelius B, Ekstrom K, Hoffman K, *et al*. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 1997, **8**, 163–168.
3. Klein HO. Long-term results with FAMTX (5-fluorouracil, adriamycin, methotrexate) in advanced gastric cancer. *Anticancer Res* 1989, **9**, 1025–1026.
4. Waters JS, Ross PJ, Popescu RA, *et al*. New approaches to the treatment of gastro-intestinal cancer. *Digestion* 1997, **58**, 508–519.
5. Douillard JY, Cunningham D, Roth AD, *et al*. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000, **355**, 1041–1047.
6. Saltz LB, Cox JV, Blanke C, *et al*. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000, **343**, 905–914.
7. Futatsuki K, Wakui A, Nakao I, *et al*. Late phase II study of irinotecan hydrochloride (CPT-11) in advanced gastric cancer. CPT-11 Gastrointestinal Cancer Study Group. *Gan To Kagaku Ryoho* 1994, **21**, 1033–1038.
8. Kohne CH, Catane R, Klein B, *et al*. Irinotecan is active in chemonaive patients with metastatic gastric cancer: a phase II multicentric trial. *Br J Cancer* 2003, **89**, 997–1001.
9. Boku N, Ohtsu A, Shimada Y, *et al*. Phase II study of a combination of irinotecan and cisplatin against metastatic gastric cancer. *J Clin Oncol* 1999, **17**, 319–323.
10. Ajani JA, Baker J, Pisters PW, *et al*. CPT-11 plus cisplatin in patients with advanced, untreated gastric or gastroesophageal junction carcinoma: results of a phase II study. *Cancer* 2002, **94**, 641–646.
11. Ajani JA, Baker J, Pisters PW, *et al*. Irinotecan/cisplatin in advanced, treated gastric or gastroesophageal junction carcinoma. *Oncology (Huntingt)* 2002, **16**, 16–18.
12. Blanke CD, Haller DG, Benson AB, *et al*. A phase II study of irinotecan with 5-fluorouracil and leucovorin in patients with previously untreated gastric adenocarcinoma. *Ann Oncol* 2001, **12**, 1575–1580.
13. Findlay MPN, Ackland S, Gebski V, *et al*. Phase II study of irinotecan, leucovorin, and 5FU (ILF) in advanced gastric cancer. *Proc Am Soc Clin Oncol* 2001, **20** [Abstract 655].
14. Pozzo C, Bugat R, Peschel C, *et al*. Irinotecan in combination with CDDP or 5-FU and folinic acid is active in patients with advanced gastric or gastro-oesophageal junction adenocarcinoma: final results of a randomised phase III study. *Proc Am Soc Clin Oncol* 2001, **20** [Abstract 531].
15. Bouche O, Raoul JL, Giovaninini M, *et al*. Randomized phase II trial of LV5FU2, LV5FU2-cisplatinum or LV5FU2-irinotecan in patients (pts) with metastatic gastric or cardial adenocarcinoma (MGA): final results of study FFCD 9803. *Proc Am Soc Clin Oncol* 2003, **22** [Abstract 1033].
16. Moehler M, Siebler J, Hoehler T, *et al*. Safety and efficacy of CPT-11/FA/5-FU (ILF) versus ELF in previously untreated advanced or metastatic adenocarcinoma of the stomach or gastrooesophageal junction. *Proc Am Soc Clin Oncol* 2003, **22** [Abstract 1034].
17. Schleucher N, Tewes M, Wilke HJ, *et al*. Phase I/II study with weekly infusional high-dose 5-fluorouracil/leucovorin/irinotecan in combination with biweekly cisplatin as first-line chemotherapy for metastatic gastric carcinoma. *Proc Am Soc Clin Oncol* 2003, **22** [Abstract 1378].
18. Assersohn L, Brown G, Cunningham D, *et al*. Phase II study of irinotecan and 5-fluorouracil/leucovorin in patients with primary refractory or relapsed advanced oesophageal and gastric carcinoma. *Ann Oncol* 2004, **15**, 64–69.
19. Shirao K, Shimada Y, Kondo H, *et al*. Phase I–II study of irinotecan hydrochloride combined with cisplatin in patients with advanced gastric cancer. *J Clin Oncol* 1997, **15**, 921–927.
20. Couteau C, Risse ML, Ducreux M, *et al*. Phase I and pharmacokinetic study of docetaxel and irinotecan in patients with advanced solid tumors. *J Clin Oncol* 2000, **18**, 3545–3552.
21. Dank M, Zaluski J, Barone C, *et al*. CPT-11 plus 5-fluorouracil (5-FU)/leucovorin (LV) versus cispaltinum (CDDP) plus 5-FU: a randomized, multinational phase III study in first-line metastatic and locally recurrent gastric cancer (MGC). *Proc Am Soc Clin Oncol* 2003, **22** [Abstract 1000].