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Short Report

Intravenous Irinotecan Plus Oral Ciclosporin

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ABSTRACT:
We previously reported a phase I study of intravenous irinotecan plus oral ciclosporin, in which dose-limiting diarrhoea was not observed, supporting the hypothesis that pharmacokinetic modulation of irinotecan by ciclosporin may improve its therapeutic index. We now report results of a further 34 patients treated at the recommended dose. A low rate of diarrhoea of grade 3 or above (3%) was again seen, with useful anti-tumour activity. The regimen is to be formally evaluated as part of a future phase III trial. Vasudev, N. S. *et al*. (2005). *Clinical Oncology* **17,** 646–649

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Introduction

Irinotecan (CPT-11) is one of the most widely used cytotoxic drugs to have been introduced in the past 10 years. It is best established in the treatment of patients with metastatic colorectal cancer: it is approved in many countries in combination with fluorouracil plus leucovorin as a first-line treatment option for this disease, or as second-line monotherapy, after failure of either fluorouracil plus leucovorin or fluorouracil plus leucovorin and oxaliplatin. Irinotecan is also being investigated in the management of several other common solid cancers, including lung and upper gastrointestinal cancer [1,2].

The dose-limiting toxicities of irinotecan are delayed diarrhoea, typically developing around 5 days after the infusion, and myelosuppression. Diarrhoea is seen with single-agent irinotecan and in combination with bolus fluorouracil plus leucovorin, although it is less of a problem with infusional fluorouracil plus leucovorin. The combination of diarrhoea and neutropenia can lead to significant morbidity and occasional toxic deaths [3]. Strategies to reduce rates of drug-related diarrhoea are, therefore, desirable.

Irinotecan is a pro-drug, converted *in vivo* to its active metabolite, SN38 (Fig. 1). In turn, SN38 undergoes inactivation by glucuronidation in the liver, and both SN38 and its glucuronide, SN38G, are cleared by biliary transport into the small bowel. Here, bacterial β-glucuronidase can convert SN38G back to SN38, which is reabsorbed, resulting in an enterohepatic re-circulation loop [4]. The presence of SN38 within the small bowel is thought to account for the delayed diarrhoea characteristic of irinotecan [5]. Altered irinotecan toxicity has been reported in association with genetic variants of the glucuronidating enzymes UGT1A1, UGT1A7 and UGT1A9 [6].

Ciclosporin, among its other effects, inhibits the biliary excretion pumps cMOAT and MDR1, and profoundly alters the pharmacokinetics of irinotecan [7]. In a recent pharmacokinetic and dose-escalation study in our unit, recommended doses of irinotecan plus oral ciclosporin were established in patients with metastatic colorectal cancer. The regimen was well tolerated, with reduced rates of severe diarrhoea [8]. We now present data for irinotecan plus oral ciclosporin in an additional 34 patients, to further define the toxicity profile and efficacy of this regimen in preparation for a proposed randomised-controlled trial.

Patients and Methods

After completing a phase I and II trial of irinotecan plus oral ciclosporin in our unit in December 2000 [8], irinotecan plus oral ciclosporin was adopted as an alternative option for patients whose standard treatment would otherwise be single-agent irinotecan. All patients treated with irinotecan plus oral ciclosporin between January 2001 and April 2003 are included in this report.

Eligibility for the regimen was as for the preceding phase I/II trial: age > 18 years; WHO performance status 0–2; white blood cell count $> 3.0 \times 10^9$/L; platelet count $> 100 \times 10^9$/L; glomerular filtration rate (estimated using the Cockcroft formula, or measured by ethylene-diaminetetraacetic acid clearance) ≥ 60 mL/min; bilirubin

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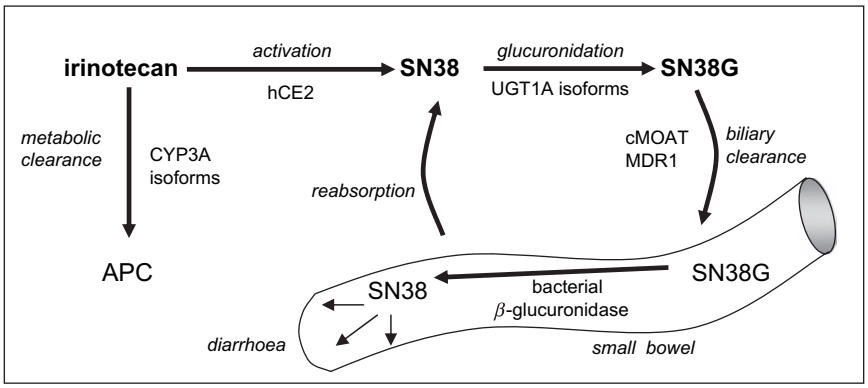

Fig. 1 – The metabolism and clearance of irinotecan.

$\leq 1.25 \times$ upper limit of normal; transaminase $\leq 3 \times$ upper limit of normal. Informed consent was obtained, including explanation of the status of the new regimen, and patients were offered the choice of receiving standard single-agent irinotecan if preferred.

Patients received irinotecan at 100 mg/m^2 every 2 weeks. Oral ciclosporin was given at 5 mg/kg every 12 h for 3 days starting the day before each irinotecan administration. Toxicity from the previous cycle of chemotherapy was recorded at each visit using NCI CTC Criteria. Treatment was paused after six cycles for computed tomography scan and clinical reassessment; patients with stable or responding disease at that point were considered for continuation of treatment.

Results

Thirty-five patients were treated. One patient, whose records could not be traced, received only one dose then defaulted for unknown reasons and died over 7 weeks later with disease progression. The primary tumour site in the remaining 34 patients was as follows: colorectal ($n = 30$); gastroesophageal ($n = 2$); adenocarcinoma of unknown primary ($n = 1$); and invasive-type pseudomyxoma peritonei ($n = 1$). All patients had received at least one prior palliative chemotherapy regimen. Among the colorectal patients, 14 (47%) had previously been treated with oxaliplatin in addition to fluorouracil (Table 1).

Twenty-two (65%) patients had progressed during their last chemotherapy. Six patients (18%) had progressed within 4 months of stopping chemotherapy, and five (15%) after more than 4 months. One patient had stopped fluorouracil after one cycle due to angina, without progression. The median interval between starting first-line palliative chemotherapy and starting irinotecan plus oral ciclosporin was 9.8 months (range 0.7–41.4 months). The median interval between the last chemotherapy administration and starting irinotecan plus oral ciclosporin was 9 weeks (range 3–38 weeks).

A total of 175 cycles of irinotecan plus oral ciclosporin were delivered (median five per patient). Twelve patients (35%) completed six or more cycles. Reasons for stopping before six cycles were progressive disease ($n = 6$; 18%); clinical deterioration ($n = 6$); intolerance of ciclosporin ($n = 6$); and other toxicity ($n = 3$). One patient was stopped electively after five cycles.

Serious adverse-event data were available for all 175 cycles, and complete toxicity data were available for 110 cycles of irinotecan plus oral ciclosporin. Ten cycles were delayed as a result of toxicity (neutropenia [$n = 8$], neutropenic sepsis [$n = 1$] and diarrhoea [$n = 1$]). A dose reduction of irinotecan was required in nine (26%) patients at some point in their treatment, most commonly for

Table 1 – Patient characteristics

Number	34
Sex (male : female)	27 : 7
Age: median (range in years)	56.5 (34–76)
Primary site	
Colon*	18
Rectum	12
Oesophagogastric	2
Other†	2
Sites of metastasis	
Liver	22
Lung	12
Other	18
Number of prior palliative chemotherapy regimens	
1	29
2	3
3	2
Prior chemotherapy	
Adjuvant (fluorouracil/leucovorin)	10
Palliative (with or without adjuvant)	34
Fluorouracil/leucovorin only	20
With oxaliplatin	15
With mitomycin	4
Epirubicin/cisplatin/5-fluorouracil‡	3

*Includes one appendiceal carcinoma. †One adenocarcinoma of unknown primary; one invasive pseudomyxoma peritonei. ‡Two patients with oesophagogastric tumours; one unknown primary.