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Initial Clinical Experience with Oral Ftorafur and Oral 6R,S Leucovorin in Advanced Colorectal Carcinoma

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FTORAFUR IS a fluoropyrimidine precursor of 5-fluorouracil. It is active orally and can be given in divided doses daily to simulate a protracted infusion of 5-fluorouracil. Against colorectal carcinoma at a dose of 750–1250 mg/m^2/day for 14-21 days it gave a response rate of 29% in 21 patients in a study by Ansfield *et al.* [1]. The co-administration of leucovorin increases the response rate of 5-fluorouracil in colorectal carcinoma by approximately 3-fold [2, 3]. Oral leucovorin is effective in modulating 5-fluorouracil activity in colorectal carcinoma [4]. The possible modulation of oral ftorafur by oral leucovorin is, therefore, of interest.

In a preliminary evaluation we gave daily oral ftorafur with intravenous leucovorin to patients with colorectal carcinoma. Partial responses were seen in 4/8 patients. We have now evaluated oral ftorafur with oral leucovorin in a phase I trial. 20 patients with colorectal carcinoma and no prior therapy received a minimum of two 21-day courses of oral ftorafur, three times daily (9 a.m., 3 p.m. and 9 p.m.) with oral leucovorin five times daily at 7 a.m., 8 a.m., 9 a.m., 3 p.m. and 9 p.m. [495 mg, daily dose; kindly supplied by Lederle (U.S.A.) Division of American Cyanamid]. The subdividing of the morning dose was based on the plateau of gastrointestinal absorption of leucovorin [5]. The starting dose of ftorafur was 1200 mg/day with escalation to 1600 and 2000 mg/day.

Toxicity is shown in Table 1. Stomatitis and diarrhoea were dose limiting. The maximum tolerated dose (MTD) was 1600 mg/day of ftorafur (~ 900 mg/m^2/day). Responses were seen in 5 patients (1 CR, 4 PR; RR 25%). Duration was a median of 8 months (range 5–10 months).

Pharmacokinetics were determined in 5 patients. Plasma ftorafur and 5-fluorouracil were measured by HPLC after an 800 mg dose of ftorafur [6]. Pharmacokinetic parameters were calculated using the LAGRAN program [7]. Mean values ± S.D. for ftorafur and 5-fluorouracil were, respectively: area under the concentration × time curve (AUC, μg.ml/h) 237 ± 9.3, 3.9 ± 1.5; mean residence time (h) 10.7 ± 1.3, 4.04 ± 1.1; time to maximum plasma concentration (h) 2.4 ± 0.2, 2.4 ± 0.7. Mean values ± S.D. for ftorafur were: plasma clearance (l/h) 3.1 ± 0.2; renal clearance (l/h) 0.6 ± 0.1; volume of distribution at steady state (l) 11.4 ± 1.3. Time to maximum plasma concentration of 5-fluorouracil was reached at 2.2 ± 1.2 h.

Thymidylate synthase activity [8] in tumour biopsy samples from 5 patients before, and again after treatment showed a decline in 2 patients, one of whom showed a PR.

The data indicate that oral ftorafur with oral leucovorin is an active regimen with tolerable toxicity at a ftorafur dose of 1600 mg/day (~ 900 mg/m^2) in divided doses (800, 400 and 400 mg). The contribution of leucovorin to the activity of ftorafur in colorectal carcinoma could not be determined in this preliminary single arm study.

The pharmacokinetic data are in line with previously reported data for oral ftorafur. Anttila *et al.* [9] found a mean AUC of 726 μg/ml/h after a dose of 2 g of ftorafur, which would correspond with 290 μg/ml/h for an 800 mg dose.

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Table 1. *Toxicity*

Dose of ftorafur (mg/day)	*N*	No. of courses (no. incomplete)	No. of courses with toxicity (no. with GR III toxicity)					
			Stomatitis	Diarrhoea	N/V*	AP†	Leucopenia	Parasthesias
1200	5	12 (3)	3 (1)	2	2	1	2	1
1600	10	27 (15)	11 (5)	7 (2)	5	5	1	1
2000	5	5 (5)	3 (2)	3	1 (1)	1	—	—

*N/V = nausea and vomiting; †AP = abdominal pain.

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Neurotoxicity After Chemotherapy With Vinorelbine

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VINORELBINE (VNB) is a semi-synthetic 5′nor-vinca alkaloid whose interesting antitumor activity seems coupled with mild toxicity. Leukopenia has been reported as the dose-limiting factor and neurotoxicity is characterised by constipation (40%) and paralytic ileus (1.5%).

We evaluated 27 patients with advanced solid cancers, most of them previously treated with radiotherapy and/or chemotherapy, who received VNB at the recommended weekly dose of 30 mg/m^2 (25 mg/m^2 in 4 patients with poor performance status and/or past heavy treatments), given in 20 min infusion without routine prophylactic antiemetics. The median number of administrations was 4 (range 1–11).

Toxicity was evaluable in 24 patients, as 3 were lost to follow-up after the first administration. According to WHO criteria, the worst haematological toxicity was grade III leukopenia in 4 previously chemo-treated patients. Peripheral neurotoxicity was negligible (grade I in 1 patient), but constipation emerged as the most prominent toxic effect in 7 patients (30%), two of them (9%) presented clinical signs of paralytic ileus. Particularly, constipation occurred at grade II–III after one administration in 3 previously untreated patients and with grade III in 2 patients who had received cisplatin-based chemotherapy; grade IV was observed after one administration at 25 mg/m^2 in 2 patients (breast and head and neck cancer), both treated earlier with heavy and prolonged chemotherapy. Symptoms recovered without sequelae after VNB discontinuation, but hospital admission and supportive care were needed in the latter 2 patients, whose paralytic ileus-related symptoms completely recovered after 5–7 days.

More toxic side-effects included nausea, grade II hair loss and moderate phlebitis on the site of injection.

The percentage of constipation cases we observed is consistent with other published data, but the grade was unexpected. All patients affected with constipation had neither particular neuropathological risk factors nor took narcotics prior or during chemotherapy, thus the onset of such an intense neurotoxicity remains unclear. Previous treatments with neurotoxic drugs seem a reasonable explanation but this does not apply to untreated patients. In summary our experience has confirmed VNB as an interesting drug with significant activity in advanced and pretreated patients (data not shown and to follow) but less manageable than expected. Myelotoxicity was not as severe in our case series as reported in the literature. We might conclude with a word of caution when VNB is planned in patients previously treated with potentially neurotoxic drugs.

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