Table 1. High-dose folinic acid, 5-fluorouracil bolus and continuous infusion in metastatic colorectal cancer: results and tolerance of a 2-day/2-week (LV5FU2) and a 3-day/3-week (LV5FU3) regimen

Regimen	N	Response (%)	Grade 2+ toxicity (%)	Mucositis (%)	Reference
LV5FU2	37	54.1	2.7	0	3
LV5FU2	42	37.0	0	8.0	4
LV5FU3	37	42.9	5.4	13.5	present study

order to maximise the 5FU dose and to avoid the cumulative toxicity of consecutive 5 day regimens. This present study was performed to investigate whether a less demanding regimen (3-day/3-week schedule, LV5FU3), would obtain similar results.

Between October 1987 and January 1989, 37 previously untreated patients with measurable metastatic colorectal cancer received a 2 h intravenous infusion of high-dose folinic acid (200 mg/m^2), followed by a 5FU 400 mg/m^2 intravenous bolus and 400 mg/m^2 in an intravenous 22 h continuous infusion on day 1, and repeated on days 2 and 3 every 3 weeks. Mean age was 61.5 years (S.D.: 10 years, range 40–80), M/F ratio 21:16. Performance status (WHO) was 0–1 in 30 patients, 2–3 in 7. Primary localisation was the colon in 31 patients and rectum in 6 patients. 26 showed liver metastases, 10 peritoneal carcinomatosis and 7 lung metastases. The largest tumours were < 2cm in 5 patients, 2–5 cm in 19, 5–10 cm in 9 and > 10 cm in 4 (computed tomography scan). Median follow-up time was 36.8 months in July 1991. We observed four complete responses (WHO definition), 11 partial responses, stable and progressive disease in 15 and 5 patients, respectively. 2 patients were not evaluable. Median duration of response was 12 months (range 5–41+). Median survival was 17 months; 34% patients were alive at 2 years and 19.5% at 3 years. Median survival in responders was 33 months and one complete responder remained disease-free at 41+ months. Grade 1–2 mucositis was observed in 5 patients (13.5%), grade 1–2 nausea/vomiting occurred in 4 patients (10.8%), grade 2 diarrhoea in 3 patients (8.1%) and grade 1–2 alopecia in 4 (10.8%). 1 patient experienced grade 1 hand–foot syndrome and another grade 3 (5.4%). One patient presented grade 3 neutropenia (2.8%).

With 43% response and 17 months median survival, the LV5FU3 regimen is active against metastatic colorectal cancer with low toxicity. However, LV5FU3 obtains results and tolerance which are not superior to LV5FU2 (Table 1). In our opinion, the LV5FU2 schedule should be preferred. A multicentre randomised phase III study is in progress to compare LV5FU2 with the 5-day/4-week bolus of 5FU and low dose bolus folinic acid regimen reported by Poon *et al.* [1].

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Eur J Cancer, Vol. 28, No. 2/3, pp. 612–613, 1992.
Printed in Great Britain
0964–1947/92 $5.00 + 0.00

Intra-arterial Cisplatin in Advanced Squamous Cell Carcinoma of the Bladder

M. Wishahi

PREOPERATIVE INTRA-ARTERIAL chemotherapy for locally advanced urinary bladder carcinoma has been reported to show encouraging clinical and pathological responses in pure transitional cell carcinoma (TCC) [1–3].

Intra-arterial cisplatin prior to cystectomy has been carried out in 6 patients with locally advanced (T3, T4) squamous cell carcinoma (SCC) of the urinary bladder. Patient characteristics are shown in Table 1. The entry criteria were: T3 or T4 (WHO), no previous chemotherapy or radiotherapy, no previous or concurrent malignancies, adequate haematological parameters and normal liver and renal function. Informed consent was obtained.

Patients were evaluated by bimanual examination under anaesthesia, intravenous urography, abdominopelvic ultrasonography, computed tomography (CT) scan and histopathological examination of tumour biopsy.

The intra-arterial chemotherapy was administered through a percutaneous catheter placed in the hypogastric artery, in the site where the tumour was most florid. Cisplatin was administered (75 mg/m^2) over 30 min, and a second course was given 2 weeks later. Patients were evaluated 2 weeks after the second course.

All cases underwent radical cystoprostatectomy and urinary diversion. The surgical specimen was subjected to histopathological examination. Clinical assessment after the two courses of intra-arterial chemotherapy showed that none of the 6 patients had responded; in 4 patients there was upstaging of the disease. Operative assessment and histopathology confirmed the absence of response. In all the patients the tumour was solid, bulky and low vascularity.

Table 1. Patient characteristics, response and survival period (months)

Patient (age, sex)	Stage: Clinical	Stage: Pathological	Pathological response*	Survival
1 (36, F)	$T_3N_xM_0$	$T_3N_0M_0$	No change	25
2 (40, M)	$T_4N_1M_0$	$T_4N_1M_0$	No change	12
3 (45, M)	$T_4N_1M_0$	$T_4N_1M_0$	Upstaged	15
4 (55, M)	$T_3N_xM_0$	$T_4N_1M_0$	Upstaged	13
5 (36, M)	$T_4N_1M_0$	$T_4N_2M_0$	Upstaged	8
6 (60, M)	$T_3N_xM_0$	$T_4N_1M_0$	Upstaged	10

*No patient had a clinical response.

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Received 14 Nov. 1991; accepted 18 Nov. 1991.

These results indicate that precystectomy intra-arterial cisplatin for advanced squamous cell carcinoma of the urinary bladder is ineffective, and unduly delays cystectomy, which is currently the only effective known treatment for this disease.

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Eur J Cancer, Vol. 28, No. 2/3, p. 613, 1992.
Printed in Great Britain
0964-1947/92 $5.00 + 0.00

Treatment of Recurrent Gynaecologic Malignancies with a New Camptothecin Derivative

H. Mori, N. Itoh, H. Kondoh and T. Tamaya

THE ANTITUMOUR activity of camptothecin, a plant alkaloid isolated from *Camptotheca acuminata*, was studied in the 1970s. However, this compound has been a disappointment because of its low response rate in clinical trials and significant myelotoxicity. The demonstration that DNA topoisomerase I is the main target of camptothecin [1] has revived interest in research on camptothecin analogues as antitumour agents. A new derivative of camptothecin, 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy camptothecin (CPT-11) has been synthesised in Japan [2]. We report our preliminary experience of CPT-11 treatment for gynaecological malignancies.

Patients with recurrent gynaecologic malignancies were eligible if they had evaluable disease, projected survival greater than 2 months and had given informed consent. Exclusion criteria included leukopenia (cells < 3000/μl), thrombocytopenia (platelets < 80000/μl) and WHO performance status of 4. Patients had not received chemotherapy for at least 4 weeks. The characteristics of 4 patients entered in this study are shown in Table 1. All the patients had evaluable pulmonary metastases, which of patients 2, 3 and 4 had been refractory to prior chemotherapy. CPT-11 (150 mg/m^2; Yakult Co. Ltd., Tokyo, Japan) was dissolved in 200 ml normal saline and infused intravenously over 30 min. CPT-11 was administered by single injections every 3 weeks. The scheduled course was delayed when haematological recovery was incomplete. Response and toxicity were assessed according to the UICC-WHO criteria.

Table 1. Clinical features of 4 patients and response to CPT-11 therapy

	Patient			
	1	2	3	4
Age	59	61	45	26
Primary focus	Cervix	Cervix	Corpus	Ovary
Histology	Squamous cell carcinoma	Squamous cell carcinoma	Chorio-carcinoma	Serous cyst-adeno-carcinoma
Clinical stage	IIb	IIIb	III	IV
Initial therapy	*	†	‡	§
Prior chemotherapy	—	‖	¶	**
Performance status	1	3	1	1
Number of pulmonary metastatic nodules	4	3	10	3
Total no. of courses	6	11	4	3
Response	CR	CR	PR	PD
No. of courses required to achieve response	6	2	1	
Duration of response (weeks)	20+††	4	20+	
Curent status	Alive(−)‡‡	Alive(+)§§	Alive(+)	Alive(+)

* Radical hysterectomy plus bilateral lymphadenectomy. † Whole pelvic irradiation. ‡ Supravaginal hysterectomy. § Total anterior hysterectomy plus bilateral salpingo-oophorectomy. ‖ [platin/peplomycin/etoposide] × 1 course. ¶[Methotrexate/actinomycin D] × 3 courses. **[platin/-doxorubicin/cyclophosphamide] × 5 courses. CR = complete response; PR = partial response; PD = progressive disease. †† (+), still responding. ‡‡ (−), with no evidence of disease. §§ (+), with disease.

As shown in Table 1, 2 complete responses (patients 1 and 2), 1 partial response (patient 3) and 1 progressive disease (patient 4) were observed. The principal toxicity was myelosuppression. Patients 1 and 2 developed leukopenia grade III and II, respectively. In these patients, the nadir was observed on day 7 after each course, resolving 2 to 4 weeks later. Patients 3 and 4 had grade I leukopenia. However, no patients developed neutropenic fever. Grade II alopecia was also noted in all patients. No renal, hepatic or cardiac toxicity was encountered.

Although the number of patients studied was small, the clinical impression was that CPT-11 was especially effective against pulmonary metastasis. CPT-11 is a unique drug that interferes with the function of DNA topoisomerase I and is notable for its non renal toxicity. CPT-11 may have significant clinical advantages for patients unable to receive cisplatin.

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Received 2 Sep. 1991; accepted 18 Oct. 1991.

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