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Letters

A Pilot Study of an Alternating Chemotherapy Regime and Sequential Radiation Therapy in Limited Stage Small Cell Carcinoma of the Lung

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UNCERTAINTY continues to exist regarding the value of combined chemotherapy and radiation therapy and the optimal sequence and timing of combined modality regimens for small cell lung cancer (SCLC). Multiple strategies and rationales for combining radiotherapy and chemotherapy have been devised including sequential, alternating and concurrent therapy [1–5].

We have investigated the combination of radiotherapy and methotrexate, vincristine, cyclophosphamide and epirubicin (MOCE-scheme A) and carboplatin, VP-16 (scheme B). The use of MOCE was based on previous experience with MOCA and MOCE [6, 7]. The cisplatinum–etoposide, as well as the carboplatin–etoposide combination is active against SCLC including patients whose disease has failed to respond to CAV or who have relapsed within a few months of completing induction chemotherapy with this regimen. Carboplatin is less toxic than cisplatinum and its administration much easier, so it is considered reasonable to use carboplatin as a substitute for cisplatinum in the front-line treatment of limited stage (LS) SCLC [2, 8]. Between January 1988 and January 1990 52 patients were treated with chemotherapy, thoracic radiotherapy and in case of complete response, prophylactic cranial irradiation. 51 were male and 1 was female, with a median age of 62 years (range 43–75). Patients were required to have a histological diagnosis or an unequivocal cytological diagnosis of SCLC and be previously untreated with chemotherapy or radiotherapy. Patients with LD were eligible. LD was defined as tumour confined to one hemithorax and/or ipsilateral or contralateral hilar or supraclavicular lymph nodes and/or documented pleural effusion.

The following alternating chemotherapy regime was used: days 1 and 15, methotrexate 50 mg/m^2 intravenously (i.v.), cyclophosphamide 500 mg/m^2 i.v., vincristine 1.4 mg/m^2 i.v. and epirubicin 30 mg/m^2 i.v. (scheme A). Day 29, carboplatin 300 mg/m^2 i.v., infusion, days 30 and 31 VP-16 250 mg/m^2 orally/day (scheme B). The whole treatment was repeated starting on day 50. Induction chemotherapy consisted of six cycles of treatment (ABABAB) unless progression of disease occurred. Patients were restaged after six cycles. Those who obtained a complete or partial response received thoracic radiotherapy. Thoracic radiotherapy was initiated 2 weeks after completion of chemotherapy. The target volume included the primary tumour with a 2.0 cm margin. The chest X-ray and the computed tomography scan of the chest obtained before the initiation of chemotherapy were used to define the primary tumour. The ipsilateral hilum and the mediastinum were included. Supraclavicular irradiation was not routinely given. A 6 MeV accelerator was used. Each fraction consisted of 2.0 Gy to midplane. The total dose was 44 Gy, delivered in 4.5 weeks in 22 fractions. Both antero-posterior and postero-anterior ports were used daily. No posterior spinal cord blocks were used. Patients achieving a complete response on re-evaluation, defined as disappearance of all clinical, radiological and other laboratory evidence of disease, received prophylactic cranial radiotherapy, starting 1 week after the completion of thoracic radiotherapy. Thirty grays in 10 fractions over 2 weeks were given to the entire intracranial contents, protecting the eyes. There was no maintenance therapy.

This report provides an analysis of the trial, performed in January 1991, with a minimum of 1 year follow-up for all patients. The complete response rate was 50% [95% confidence interval (CI) 78–48] and the partial respone rate was 28% (95% CI 51–21). The overall response rate was 78% (95% CI 89–67). Twelve per cent of the patients (95% CI 32–10%) developed progressive disease. The medium duration of complete response was 15+ months (range 4–24+) and of partial response was 6 months (range 2–18). The median duration of survival was 21.7+ months for complete responders, 12.3 months for partial responders and 10 months for those who developed progressive disease. Twenty-three per cent of the patients were alive two years after the start of chemotherapy (Fig. 1). Liver (60%), bone (33%), adrenals (20%), lymph nodes (10%) and chest (8%) were the most common sites of relapse. Nobody has relapsed in the brain so far.

Toxicity was moderate for all patients. There were no treatment-related deaths or treatment-related hospital admissions. No neurological sequelae, related to brain irradiation, have been observed.

The results of this study using sequential radiation therapy suggest that there is no significant improvement in the prognosis of SCLC with the addition of radiation therapy 23 weeks after the beginning of chemotherapy. The local relapse rate was satisfactory. The toxicity was moderate and the quality of life of most patients was good.

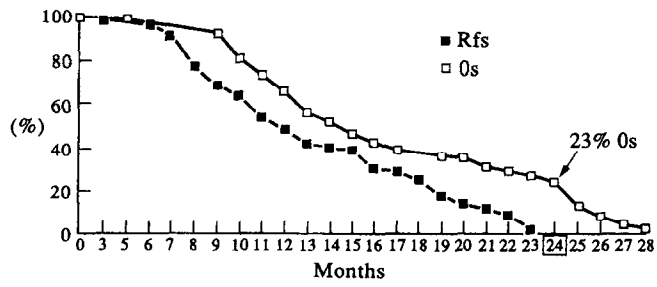

Fig. 1. Relapse-free survival (Rfs) and overall survival (Os).

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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.