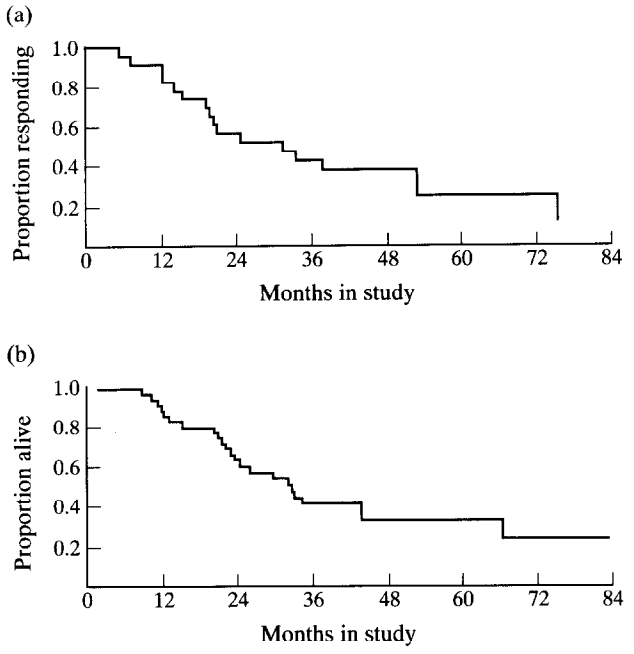

Figure 1. Response duration (a). Overall survival (b).

infiltrating ductal carcinoma. 17 patients had >10 axillary nodes. 21 patients (58%) had received endocrine therapy. 21 patients (58%) had previous cyclophosphamide–methotrexate–5-fluorouracil CT (12 adjuvant and 9 for metastases). 17 patients (47%) had received radiotherapy for palliation. A mean of 7.5 CT courses were administered to each patient. Median follow-up was 33 months.

Toxicity of CT was mainly haematological, with fifteen patients having grades 2–3. 16 patients had grade 2 gastrointestinal toxicity. Toxicity of maintenance therapy was mild, and mainly hepatic.

11 patients had a complete response (CR) (31%), 12 had a partial response (PR) (33%), 7 had stable disease (19%), while 6 had progressive disease (17%) (overall response rate 64%, 95% CI 48–80%). A CR was observed in 3 patients that had a PR to CT alone (two liver and one bone metastases) after 3 months of maintenance therapy. Responses were achieved in bone (8 patients), soft tissue (5 patients) and viscera (10 patients). As of December 1993, 33% of patients were alive, and median response duration and overall survival were 31 (range 5–75) and 32 (range 9–83) months, respectively (Figure 1). 2 patients with cutaneous lesions and PR had an increase of ER tumour content from 60 to 90% and from 40 to 80% of cells during maintenance therapy.

Due to the tumour heterogeneity, CT is capable of eradicating sensitive, actively proliferating cell clones. Disease may relapse in the presence of CT-resistant, slowly proliferating cells (minimal residual disease). Retinoid analogues of vitamin A, such as TAM, enhance the secretion of transforming growth factor-β which inhibits growth of most epithelial cells [7]. Synergism of action has been shown for retinoids and IFN in advanced squamous carcinomas of the skin and the cervix [8, 9]. The action of IFN and retinoids could be synergistic with TAM in inhibiting the regrowth of minimal residual disease. In the present trial, we obtained a 64% response rate and a median response duration and survival of 31 and 32 months, respectively, without affecting quality of life. In conclusion, it is possible to administer CT and immuno-hormonotherapy sequentially with acceptable toxicity, and to prolong response duration.

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Dose Intensification of Carboplatin and Etoposide as First-line Combination Chemotherapy in Small Cell Lung Cancer

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CISPLATIN COMBINED with etoposide (EP) is one of the most effective first-line regimens in small cell lung cancer (SCLC) [1, 2], although the cisplatin component can be associated with significant toxicity [1]. Our group has previously tested the less toxic cisplatin analogue carboplatin [3] in combination with etoposide (CE) in SCLC reporting high response rates [4], results which have been subsequently confirmed by others [5, 6]. In

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our original study, response duration was disappointingly short, possibly due to suboptimal dosing. The aim of this pilot study was to examine the effect of moderate dose escalation of carboplatin and etoposide in improving survival, whilst maintaining a satisfactory toxicity profile.

From August 1989 to May 1993, 54 consecutive previously untreated patients were entered into the study having met the following inclusion criteria: histologically or cytologically proven SCLC, normal full blood count (FBC), satisfactory renal function ([^{51}CR]EDTA clearance > 60 ml/min), WHO performance status (PS) < 3. Patients with cerebral metastases were not excluded. Local ethical committee approval and signed informed consent from all patients were obtained. Median age was 58 years (range 36–74). 28 patients had limited disease (LD) and 26 extensive disease (ED). Median performance status was 1 (range 0–3). Pretreatment staging investigations included FBC, biochemistry, chest X-ray (CXR) (computed tomography (CT)) thorax if disease not measurable on CXR), ultrasound or CT liver and [^{51}CR]EDTA clearance. Bone scan, bone marrow aspiration, and CT brain were only performed when clinically indicated. Patients had FBC, biochemistry, and CXR prior to each treatment and nadir FBC day 10–14. Restaging of chest and upper abdomen and other known sites of disease was performed following four cycles of treatment.

Chemotherapy consisted of carboplatin (C) 600 mg/m^2 i.v. (intravenous) on day 1, and etoposide (E) 120 mg/m^2 i.v. on days 1–3 for two 28-day cycles, followed by an elective dose reduction to C 400 mg/m^2 and E 100 mg/m^2 for a further two cycles in responding patients. The first 7 patients were treated on either cycle 1 or cycle 2 with an experimental growth factor as part of a multicentre trial. This was found to be ineffective and the trial discontinued [8]. A 25% dose reduction of C was made if WHO grade (Gd) 3/4 neutropenia occurred in the setting of neutropenic infection, or if Gd 3/4 thrombocytopenia occurred requiring platelet transfusion. Following chemotherapy, responding LD patients received thoracic irradiation, and patients obtaining CR were randomised to receive prophylactic cranial irradiation or no further treatment as part of an ongoing multicentre trial.

46 (87% 95 CI 78–96) of 53 assessable patients (1 patient died of myocardial infarction on day 15) obtained an objective response with 15 CRs (28%) and 31 PRs (59%). Response rate for LD patients was 93% (95 CI 83–100) with 52% CR, and 81% (95 CI 66–96) for ED patients with only 1 patient (4%) achieving CR. Median response duration was 9 months for LD patients and 6 months for ED patients. 29 patients (55%) received second-line chemotherapy at the time of relapse. In the great majority (24 patients) this was with ACE (doxorubicin, cyclophosphamide, etoposide). 12 patients (41%) obtained PRs with a median response duration of 5 months. Median survival was 14.5 months for LD patients and 9 months for ED patients. Predicted 2-year survival for LD patients was 18%.

Haematologic toxicity was the main adverse feature of this treatment, with two thirds of the patients developing Gd 3/4 leucopenia and/or thrombocytopenia. 28 patients (53%) developed neutropenic fever at some stage during treatment, 4 (8%) had life-threatening infection and there were two toxic neutropenic deaths. Non-haematological toxicity was minimal, with Gd 1/2 nausea and vomiting the most common problem. Table 1 shows a detailed outline of the toxicity profile. 12 patients (23%) required a dose reduction during chemotherapy for either severe neutropenia or thrombocytopenia, with 2 requiring a further dose reduction on the following treatment cycle because of neutropenic fever.

Table 1. Toxicity: worst grade for all courses

	WHO Grade						
	0	1	2	3	4	%1–2	%3–4
Haematological							
WBC	3	4	9	19	18	24	69
Platelets	12	2	4	11	24	11	66
Non-haematological							
Infection	24	8	12	5	4	38	17
Nausea/vomiting	16	23	10	4	0	62	8
Mucositis	34	12	6	1	0	34	2
Diarrhoea	43	5	2	3	0	13	6
Alopecia	0	2	8	43	0	19	81
Neuropathy	49	4	0	0	0	8	0
Nephrotoxicity	48	0	4	1	0	8	2

This study reveals that moderate dose intensification of carboplatin and etoposide can be achieved with minimal non-haematological toxicity and easily manageable haematological toxicity with standard supportive care. It further confirms the high activity of carboplatin and etoposide in SCLC, and our results in terms of survival are similar to those from other reported series using either CE [5, 6] or EP [2, 8] although inferior to others [9]. Response duration remains disappointingly short, particularly for LD patients. It is possible that the staging investigations in this study which are less extensive than in some reported series [9] may have underestimated disease extent and contributed towards a less impressive outcome for LD patients.

Dose intensification to these doses does not appear to confer any appreciable survival benefit compared with conventional doses of other regimens, and there seems little to be gained by taking this regimen forward to be randomised against standard treatments such as cisplatin/etoposide.

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