Table 1. Responses according to histological type

Tumour type (No. pts)	Tumour responses (%) CR	PR	NC	PD
Anaplastic (11)	2 (18)	-	1 (9)	8 (73)
Non-anaplastic (9)	-	1 (11)	6 (67)	2 (22)

CR, complete remission; PR, partial remission; NC, no change; PD, progressive disease.

4–20). 10 patients progressed and 50% of these had clear disease progression after only one cycle of chemotherapy. Table 1 shows antitumour activity according to the histological type. Median survival was 2 months (range 0.5–17+) in patients with anaplastic carcinoma and 22 months (range 3–38+) in the non-anaplastic carcinoma.

The association of epirubicin and carboplatin was well tolerated, but an overall response rate of 15% calls for a need to identify new drugs or new approaches for the treatment of thyroid carcinoma, especially considering that such tumours comprise different morphologies, natural histories and prognoses [9, 10]. Consequently, it is important to consider the histological type. In our analysis, we considered two different subgroups, anaplastic and non-anaplastic tumours, which showed different relationships with chemotherapy.

It appears that chemotherapy did not impact on the natural history of non-anaplastic carcinomas because 67% of treated patients had stable disease, with a median duration of 10 months (range 4–20) and a median survival of 22 months (range 12+–38+), and no complete remissions were obtained in this subgroup of patients. However, patients with anaplastic carcinoma might benefit from chemotherapy as suggested by the 2 complete remissions lasting more than 1 year in this study, with a median survival of 2 months. Nevertheless, in the same group, 45% of patients experienced early progression, with a median survival of 41 days (range 13–58).

Therefore, there is a need to select patients with non-anaplastic carcinoma avoiding treatment of asymptomatic cases with indolent disease. Clinical and biological prognostic factors for response must be identified for anaplastic carcinomas because of their bimodal response to treatment.

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Phase II Study of Intensive CEV (Carboplatin, Epirubicin and VP-16) Plus G-CSF (Granulocyte-colony Stimulating Factor) in Extensive Small Cell Lung Cancer

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THE DOSE intensity of chemotherapy seems to be crucial in a number of responsive tumours [1]. Earlier studies on high dose

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chemotherapy in small cell lung cancer (SCLC), a chemosensitive tumour, were encouraging, but the results cannot be generalised because of small samples and a non-randomised design. The complete response rates were high, but survival data were comparable to previous results [2,3].

Intensive chemotherapy, even when supported with corticosteroids and/or antibiotic prophylaxis, causes myelosuppression. Thus, high dose chemotherapy is usually combined with autologous bone marrow transplantation support. Most studies of this strategy have reported small samples and/or non-randomised design. In fact, response rates were high, but there was no survival advantage [4].

Recently, the introduction in clinical practice of haematopoietic growth factors caused a renewed interest in the field. Colony stimulating factors (CSF) can accelerate the recovery of myelopoiesis after chemotherapy. In randomised trials, G-CSF (granulocyte-CSF) decreased the incidence of febrile neutropenia and increased the number of courses of chemotherapy given on time in SCLC patients [5].

In previous studies, we tested the activity of a regimen consisting of carboplatin, 300 mg/m^2, i.v. (intravenous) day 1; epirubicin, 50 mg/m^2, i.v., day 1; and VP-16, 100 mg/m^2, i.v., days 1–3 repeated every 4 weeks (CEV regimen) [6,7].

In the present study, we tested the activity and toxicity of intensive CEV regimen with recombinant G-CSF support. Intensification was obtained by increasing the dose of epirubicin and VP-16 and reducing the intervals between cycles.

Eligibility criteria included histologically proven extensive SCLC, performance status (ECOG) 2 or less, age 70 years or less, no previous chemotherapy, and adequate bone-marrow, cardiac, hepatic and renal functions. Informed consent was obtained from all patients.

Doses of chemotherapy were: carboplatin, 300 mg/m^2, i.v., day 1; epirubicin, 75 mg/m^2, i.v., day 1; and VP-16, 140 mg/m^2, i.v., days 1–3. G-CSF was administered at the dose of 5μg/kg/day, days 6–15. The cycle of chemotherapy was repeated every 3 weeks. Chemotherapy was continued for a maximum of six cycles. If on day 28 of each chemotherapy course the WBC were $< 4000/mm^3$ or platelets were $< 100\,000/mm^3$, the course was delayed for a maximum of 1 week until haematological recovery. If during prior chemotherapy the leucocyte count was $< 500/mm^3$ and/or a platelets count was $< 10\,000/mm^3$, the doses of all drugs were reduced by 25%.

All patients were staged with cranial, thoracic and abdominal computer tomography (CT)-scan and bone marrow aspiration examination. All patients included were evaluated for response and toxicity according to WHO criteria.

From June 1992 to April 1994; 36 patients (33 males and 3 females) entered the study. Median age was 58 years (range 43–70). Three patients entered with a performance status (PS) of 0, 20 with PS 1 and 13 with PS 2. Overall, 192 cycles of intensive CEV were administered. 28 (77.8%) patients received all six planned cycles. Chemotherapy was stopped in 8 cases, in 6 because of progression of the disease and in 2 because of death.

Twenty-nine objective responses were recorded (response rate: 80.6%; 95% exact CL: 64.0–91.8); 10 responses were complete (27.8%; 95% exact CL: 14.2-45.2); in 2 patients the disease was stable, 5 progressed during the treatment and 2 died of sepsis prior to response evaluation. As of February 1995, with a median follow-up of 22 months, 33 (91.7%) patients progressed, of which 77.8% died. Median progression-free survival and median survival, according to the Kaplan–Meier method, were 7 months (95% CL: 6–9) and 10 months (95% CL: 8–11), respectively.

25 patients (69.4%) received the planned dose at established intervals; thus, median relative dose intensity was 1.0 and the median delivered dose intensity was 100 mg/m^2/week for carboplatin, 25 mg/m^2/week for epirubicin and 140 mg/m^2/week for VP-16.

Toxicity was severe. 2 patients died of sepsis (following the first and the fourth cycle, respectively). Grade 3 and 4 leucopenia were observed in 27.6 and 25% of cases, respectively. Grade 3 and 4 thrombocytopenia were found in 38.8 and 13.8% of patients, respectively. Grade 3 anaemia occurred in 27.6% of cases. Grade 2 nausea and vomiting occurred in 8.3% of patients. Grade 2 neurotoxicity was reported in 8.3% of cases.

The planned schedule and doses of intensive CEV should induce a 1.73 relative dose intensity as compared with standard CEV [6]. In terms of dose intensity, this phase II study successfully reached the planned end-point because 69.4% of patients received the planned dose intensity. Relative dose intensity for patients requiring cycle delay or dose reduction ranged from 1.18 to 1.64. Thus, all patients received more than standard CEV dose intensity.

Nevertheless, the activity of intensive CEV in extensive SCLC is comparable to that of standard CEV. Indeed, the response rate obtained with standard CEV was 83.6% and median survival was 10 months in a group of 49 patients within the same cooperative group as the present study [6]. Moreover, the complete response rate did not increase with intensive CEV with respect to standard CEV: 28.5% with standard versus 27.8% with intensive CEV. Toxicity, however, was more frequent and more severe with intensive than with standard CEV.

Our disappointing data with intensive chemotherapy are similar to those recently reported in the literature [8,9]. Sculier and Souhami, in two different large randomised trials, compared intensive, multiple drugs, weekly chemotherapy to a standard combination regimen [8, 9]. In both studies, toxicity was increased with intensive chemotherapy and there was no improvement in response or survival.

Miles and associates in a small randomised phase III study of intensive weekly chemotherapy with and without G-CSF, found that G-CSF did not result in a significant increase in dose intensity or in response rate, while the small sample size precluded a survival analysis [10].

However, the introduction of infusion of peripheral blood progenitor cells opens a new horizon in the field of high dose chemotherapy in SCLC, although the data regarding this new therapeutic approach are very preliminary. The exact role of high dose chemotherapy with combined haematological support (growth factors, progenitor cells, autologous bone marrow transplantation) for SCLC needs to be addressed in large randomised phase III trials.

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Oral Chemotherapy with Doxifluridine and Folinic Acid in Biliary Tract Cancer

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ALTHOUGH INFREQUENT, cancer of the biliary system is associated with a high death rate, the 5 year survival rate for unresectable disease being less than 10% and median survival 12 months [1]. Given that the majority of biliary tumours are not resectable at presentation, they are candidates for palliative treatment [2]. Unfortunately, the value of systemic and locoregional chemotherapy still needs to be established [3, 4]. Doxifluridine (dFUR) is a new fluoropyrimidine derivative characterised by a higher therapeutic index and greater cytotoxicity than other fluoropyrimidines in animal models [5]. The oral administration of dFUR leads to optimal gastrointestinal absorption, with approximately 60–80% of the drug reaching the peripheral blood unaltered [6, 7]. A recently published meta-analysis of nine studies, comparing 5-fluorouracil (FU) with FU plus leucovorin in patients with advanced colorectal cancer, has shown that the combination produces a higher response rate than FU alone [8]. Although the optimal dose of leucovorin for optimal FU modulation has not yet been assessed, the gastrointestinal absorption of leucovorin remains optimal for oral doses of no more than 50 mg [9]. On the basis of these considerations, this single-institution study was designed to evaluate the activity and feasibility of an oral regimen with low doses of levo-leucovorin and dFUR in biliary tract cancer.

The eligibility criteria included histologically confirmed unresectable or metastatic carcinoma of the biliary tract (gall bladder or bile ducts), measurable disease, no more than one line of previous chemotherapy, ECOG performance status of 0–2, age <75 years, adequate bone marrow function (WBC count >4000/mm^3, platelet count >100,000/mm^3), liver function (bilirubin <3 mg%, serum transaminases <3 times above the upper normal limit) and renal function (serum creatinine <1.5 mg%, blood urea nitrogen <50 mg/dl). Informed consent was obtained from each eligible patient. dFUR was supplied by Roche (Milan, Italy) in the form of tablets of 500 and 750 mg; leucovorin was obtained from commercial sources. The patients were treated with oral dFUR at a dose of 1200 mg/m^2 on days 1–5 every 10 days, 2 h after they had received 25 mg oral levo-leucovorin. No food or alcohol was to be taken 1 h before leucovorin until 2 h after dFUR administration. Response was assessed every six cycles according to WHO criteria. Toxicity was evaluated at every cycle and graded according to WHO criteria. In the case of grade 4 toxicity (or grade 3 on two consecutive occasions), the patients were excluded from the study. In the case of grade 3 diarrhoea or mucositis, treatment was discontinued until recovery and then restarted with a 50% reduction in the dFUR dose. 32 patients with locally advanced or metastatic biliary tract cancer were enrolled from June 1991. The main characteristics of the eligible patients are listed in Table 1. A median of ten cycles per patient were delivered, with the maximum of 36 cycles in one case. Treatment compliance was encouraging, with 265 of the 323 cycles being delivered at 100% of the dose and only 23 being delayed by 2 days or more. All of the treatment delays and dose reductions were due to diarrhoea.

5 patients achieved objective responses, including one CR and four PR (16%; 95% confidence interval 5–33%) with a median response duration of 2 months (range 1–3). The median time to response was 4 months (range 2–5). All of the responses were

Table 1. Main features of eligible patients

Eligible	32
Male/female	17/15
Median age (range)	60 (33–71)
ECOG performance status	
0/1/2	20/9/3
Pretreated with chemotherapy	5
Sites of primary	
bile ducts	22
gall bladder	10
Locally advanced	15
Metastatic	17
Sites of metastases	
liver	10
lung	6
lymph nodes	8
liver and other sites	8

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