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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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observed in previously untreated patients (18%; 95% confidence interval 5–33%) whose primary disease site was in the bile ducts. The responding lesions' sites included the liver (1), the lung (1) and the primary site (3). The median time to progression was 3 months (range 1–11); median survival in the patients as a whole was 8 months (range 1–16 months). The side-effects were manageable and always reversible. The single significant side effect was diarrhoea which was observed in 57% of cases (grade 3–4 in 22%). The median time to recovery was 7 days; in 2 cases, the side-effects persisted for more than 10 days. Hospitalisation was necessary in only one case. Although no anti-emetic prophylaxis was used, mild or moderate nausea or vomiting was observed in only 6 cases. Other toxicities included grade 1–2 abdominal pain which was observed in 30% of cases, and grade 1 hand–foot syndrome which was recorded in 25% of patients.

The activity of systemic chemotherapy in biliary tract cancer has rarely been evaluated in a large number of patients, the largest study available in the literature involving 30 patients treated with mitomycin-C [10]. The present report provides interesting data on the possibility of oral palliative chemotherapy in unresectable biliary tract cancer. Although moderate, the response rate observed in previously untreated patients (18%) is in line with the results reported in the literature [3, 4, 10] and, moreover, was observed in an adequate number of patients. It is worth noting that all the objective remissions in our series of patients were obtained in patients with primary bile duct disease, whereas no remission was observed in those with gall bladder carcinoma. However, although interesting, these data require confirmation in a larger group of patients because the small number of patients with primary gall bladder cancer in this series does not allow any definite conclusions to be drawn. Moreover, given the paucity of series reported in the literature, no data are available concerning any possible different chemosensitivity of these tumours. In summary, given the moderate activity and absence of myelotoxicity, the possibility of more complex regimens combining the proposed schedule with other drugs will be investigated in future trials.

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Long-term Survival in a Patient with Rosai–Dorfman Disease Treated with Interferon-α

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Sinus histiocytosis with massive lymphadenopathy (SHML, Rosai–Dorfman syndrome) is a rare tumorous disorder of unknown aetiology that is usually regarded as benign [1, 2]. Involvement of aberrant immune responses to viral infections, i.e. Epstein-Barr virus or human herpes virus-6 has been suggested [3, 4]. We observed a 40-year-old patient who presented in 1980 with extranodal nasal manifestation of Rosai–Dorfman disease. Cervical and mediastinal lymphadenopathy and extranodal skin eyelid and larynx tumours developed that were resected. Steroid therapy in 1983 did not prevent recurrent eyelid and larynx manifestation. Subsequently, the patient showed a partial response to CHOP chemotherapy [5]. However, in 1984, clinical and radiological restaging revealed progressive disease, when a skin biopsy showed criteria of malignancy [4, 5]. Therefore, from 1985 to 1990, the patient received three cycles of 36 miu interferon-α2a three times a week for 3–4 months. He experienced three complete remissions of all neoplasia that lasted 13–21 months. However, weight loss, depression, leucopenia and cardiac arrythmia were observed as severe therapeutic side effects. In 1991, conservative left lateral cervical dissection had to be performed owing to a recurrent laryngeal tumour. Since 1992, multiple tumour manifestations in the thyroid gland, subglottis and skin indicated massive progressive disease. In 1993, a new 4 month interferon-α trial with reduced dosage (6 miu 3 times a week) resulted in partial response, but had to

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