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SHORT COMMUNICATION

Phase II study of 5-fluorouracil (5-FU) and high dose folinic acid (HDFA) in hepatocellular carcinoma

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Nonresectable hepatocellular carcinoma (NHC) has a very poor prognosis with virtually no patients (pts) surviving 5 years from diagnosis (Moertel, 1973).

Doxorubicin is one of the most active agents in the treatment of NHC, with a median response rate of up to 25% (Friedman, 1983). However, a more recent study reported a response rate of only 10% in 109 patients, although 27% of symptomatic patients had an improvement in performance status and symptom control (Sciarrino *et al.*, 1985). 5-Fluorouracil (5-FU) as a single agent has a quite low activity in NHC with a median response rate of 20% (range 0–50%) in three different studies (Cady *et al.*, 1985); nevertheless it is included in almost all the combination regimens tested in NHC (Friedman, 1983; Cady *et al.*, 1985). Recent studies suggest that the therapeutic activity of 5-FU may be enhanced by increasing endogenous reduced folate pools *in vivo* (Rustum, 1985) and the combination of 5-FU and high-dose folinic acid (HDFA) seems quite promising in gastrointestinal malignancies (Machover *et al.*, 1986). We report here the results of a phase II study with 5-FU and HDFA performed in an attempt to improve the results obtained with 5-FU alone in NHC.

From January 1986 to March 1987 14 consecutive previously untreated patients with histologically or cytologically proven NHC were treated with the following regimen: HDFA – 200 mg m^{-2} by i.v. infusion over 2 h followed by 5-FU – 370 mg m^{-2} by i.v. infusion over 15 min daily for 5 consecutive days repeated every 4 weeks. Patients characteristics are outlined in Table I.

Eligibility requirements included an ECOG performance status ≤ 3, WBC ≥ 4000 mm^{-3}, platelet $> 100{,}000$ mm^{-3}, serum creatinine < 2 mg%, bilirubin < 2 mg%, no prior treatment and measurable disease. At the initiation of treatment full blood count, HbsAg determination, chest X-ray, liver CT scan and/or ultrasonography and alpha-foetoprotein assay were performed.

Evaluation of response took place after at least two cycles according to WHO criteria (WHO, 1979) while toxicity was assessed according to Miller's score (Miller *et al.*, 1981). Response was assessed utilizing the same techniques (liver CT and/or ultrasound, chest X-ray) performed before the start of the study.

No response was seen in any of the 14 evaluable patients; 6 had stabilization of disease for a median duration of 82 days (range 70–128) while 8 progressed. Median survival was 98 days (range 44–281) with no difference between patients with stable or progressive disease. Treatment did not influence AFP levels in any patient.

Table I Patient characteristics

Total entered	14
Total evaluable	14
Sex	
Male/female	12/2
Age (yrs)	
Median:	47.3
Range:	39–68
ECOG performance status	
Median:	2
Range:	1–3
HbsAg-positive	10/14
Concomitant liver cirrhosis	5/14
Distant metastases	4/14
Lung=	3
Nodes=	2
Soft tissues=	1
Alpha foetoprotein (IU ml^{-1})	
Median:	487
Range:	8–175,000
Histology	
Well differentiated	12
Anaplastic	2

A total of 56 cycles was administered with a median of 4 cycles for each patient (range 2–9). Nausea and vomiting were completely absent; three patients experienced grade II diarrhoea, while two patients had grade III oral mucostitis. One patients developed a partial alopecia; only one patient had a grade II granulocytopenia. In this quite homogeneous group of patients with NHC, the true response rate of HDFA + 5-FU is $< 20\%$ at the 95% confidence interval (Lee *et al.*, 1979).

Although well tolerated, the combination of HDFA and 5-FU seems unable to produce better results than 5-FU alone in NHC.

Efforts continue to seek ways to improve the outcome of NHC and all patients with primary liver cancer must be considered candidates for investigative protocols.

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