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 performed 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 and cytologically proven NHC were treated with the following regimen: HDFA – 200 mg m⁻² by i.v. infusion over 2h 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.

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 mucositis. One patient 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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Table I Patient characteristics

| Characteristic            | Total entered | Total evaluable |
|---------------------------|---------------|-----------------|
| Sex                       | 14            | 14              |
| 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|

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