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Phase II Intravenous Study of Epirubicin with 5-Fluorouracil in Patients with Advanced Hepatocellular Carcinoma

Mikael J. Kajanti and Seppo O. Pyrhönen

Between August 1986 and September 1990, 22 previously untreated non-cirrhotic patients with measurable unresectable primary liver cancer were treated every 4 weeks with a combination of epirubicin and 5-fluorouracil. The dose of epirubicin was escalated; the starting dose was 40 mg/m^2, the second dose was 50 mg/m^2 and thereafter 60 mg/m^2 during subsequent cycles. The dose of 5-fluorouracil was always 800 mg/m^2. Objective response rate was 14%. Most of the patients experienced only mild haematological toxicity, and no other dose limiting toxicity was observed. Nonetheless, increasing the dose would probably not have increased the response rate.

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INTRODUCTION

MOST PATIENTS with advanced liver (hepatocellular) carcinoma fall within the sphere of palliative treatment and are therefore candidates for chemotherapy. The most effective single agents, doxorubicin and 5-fluorouracil, have at best yielded response rates of 25% among patients with hepatoma [1]. Epirubicin (4'epidoxorubicin) is an isomer of doxorubicin with a lower cardiotoxicity [2]. Systemic intravenous therapy with epirubicin has been tested in hepatocellular carcinoma. Two phase II studies have shown response rates of 9 and 17% [3, 4]. The aim of this study was to evaluate the efficacy and toxicity of epirubicin combined with 5-fluorouracil given intravenously in advanced inoperable or metastatic hepatocellular carcinoma.

Between August 1986 and September 1990, 22 consecutive, untreated non-cirrhotic patients with measurable and histologically and/or cytologically confirmed unresectable primary liver cancer were entered on the study. All histological and/or cytological specimens were re-examined. One of the tumours was fibrolamellar. The disease was confined to the liver in 14 patients (9 males and 5 females), whereas 8 patients (5 males and 3 females) were in the metastatic phase at presentation. The mean age of all patients was 51 years (range 16–69 years). The metastatic sites were distributed as follows: lung (2 patients), bone (3), distant lymph nodes (1) and peritoneal carcinosis (2).

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Patients were required to have a Karnofsky performance status of at least 60%, be under 70 years of age, and without any other previous or current malignancy (excluding basal cell carcinoma of the skin or *in situ* carcinoma of the cervix uteri). The required pretreatment laboratory values were: WBC count >3500/μl; platelet count >120000/μl; haemoglobin >10 g/dl; and blood urea nitrogen, creatinine and bilirubin below 1.5 times normal. The criteria for exclusion were: cardiovascular and/or other diseases contraindicating for anthracycline treatment, previous chemotherapy, and/or an estimated survival time less than 6 weeks.

Patients were treated every 4 weeks. A 3 min bolus injection of epirubicin was followed by a 30 min infusion of 5-fluorouracil. The amount of epirubicin given was gradually increased: the starting dose was 40 mg/m^2, the second 50 mg/m^2, and thereafter the dose remained constant at 60 mg/m^2. As long as the nadir value of WBC was <3500/μl, or that of the platelets <100000/μl, the amount of epirubicin was not increased. The 5-fluorouracil dose was always 800 mg/m^2.

Treatment was repeated until progression was observed. Changes in liver size were monitored monthly by palpation. The state of tumours was monitored in two ways: biochemically (liver enzymes), by monthly determination of the alpha feto-protein (AFP) level, and radiologically every 3 months by computed axial tomography (CT). All the patients underwent serial CT. The antitumour effect and toxicity of the treatment were scored using WHO criteria [5]. The survival times of the patients were measured from the start of treatment. No other treatment (e.g. palliative radiotherapy) was given to the patients.

3 of the 22 patients experienced an objective response, 1 achieved a complete response (CR) and 2 partial responses (PR). The median survival time was 11.7 (S.D. 13.2) months (range 1–59 months) (Fig. 1). There were 4 patients with a measurable serum AFP level. 1 of these 4 patients experienced CR and is still alive after 59 months' follow-up. She received 12 courses of chemotherapy. Her initial AFP value was 12000 ng/ml; after seven treatments it was normal, and has since remained normal. This CR has been confirmed and is regularly followed by CT. 2 other patients with AFP+ tumours achieved PR and survived 26 and 25 months, respectively. 6 patients had disease stabilisation. They survived from 13 to 17 months. 1 of them was a 16-year-old boy, whose tumour was fibrolamellar; he survived 14 months.

The treatment given and the haematological toxicity were similar in both patients in whom the disease was confined to the liver and in patients with metastatic disease (Table 1). 1 patient with metastatic disease expired due to septic infection during the treatment. The treatment caused severe alopecia (grade 3–4) in 9 patients, despite scalp cooling. Nausea and vomiting were significant (grade 2–4) in 13 patients despite prophylactic anti-emetics (metoclopramide and lorazepam).

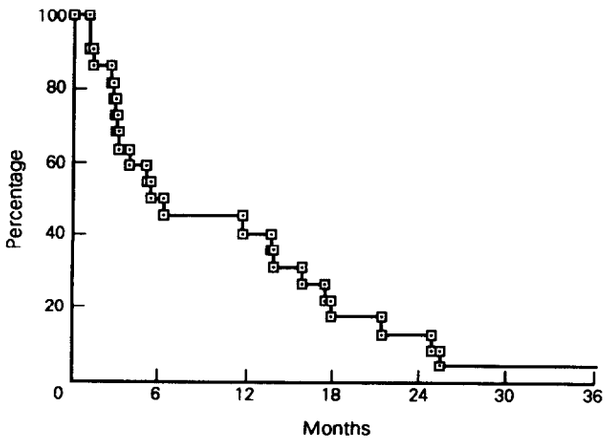

Fig. 1. Survival time from the start of treatment.

Table 1. Treatment given and toxicity

No. of patients	22
Total courses	112
Median (range) courses per patient	5 (1–12)
Median (range) cumulative dose of epirubicin (mg/m^2)	262 (50–847)
Median (range) maximum dose/cycle of epirubicin (mg/m^2)	50 (40–60)
Haematological toxicity	
(lowest per patient) WBC (cells/μl)	
nadir: median (range)	4.9 (0.9–20.5)
<3000/μl (all courses)	55/112 (49%)
Platelets (cells/μl)	
nadir: median (range)	231.000 (52.000–631.000)
<100000 (all courses)	14/112 (13%)

As a single drug, epirubicin appears to have only a minor effect on hepatocellular carcinoma [6]. The Epirubicin Study Group for Hepatocellular Cancer [7] found that this drug may yield effect much more slowly than expected and it may prolong the survival time in certain patients, without inducing any apparent tumour regression. Similar results were obtained in the present study, which combined epirubicin with 5-fluorouracil. Some studies [8, 9], however, have shown that patients with untreated hepatocellular carcinoma may survive for several years after diagnosis. 1 of our patients with AFP+ tumour achieved CR and is still alive after 59 months' follow-up. 2 other patients with AFP+ tumours survived 26 and 25 months, respectively. There is some evidence that patients with AFP+ hepatomas respond favourable to chemotherapy [10].

In a study using epirubicin as a single agent with a dose of 30 mg/m^2 every 3 weeks The Cancer and Leukemia Group B reported a 9% response rate in patients with advanced liver cancer [11]; whereas in a study using epirubicin as a single agent with a dose of 90 mg/m^2 every 3 weeks Hochster *et al.* reported a 17% response rate [3]. The response rate in this study was 14% (95% confidence limits 3–35%). Since most of the patients experienced only mild haematological toxicity, and no other dose-limiting toxicity was observed, it is likely that many of these patients could be treated using a slightly higher dose than that outlined in the protocol. Nevertheless, increasing the dose would probably not have increased the response rate significantly.

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Low-power Laserthermia for the Treatment of Small Hepatocellular Carcinoma

Guan-Tarn Huang, Teh-Hong Wang, Jin-Chuan Sheu, Norio Daikuzono, Juei-Low Sung, Mu-Zong Wu and Ding-Shinn Chen

Laserthermia by a novel interstitial probe adapted to low power Nd-YAG laser machine was used to treat small hepatocellular carcinoma (HCC). The set condition was 43–45°C in thermocouple with power of 2–3 W and the duration 20–30 min. In the 5 cases studied, 1 had a good result with total necrosis of the tumour without recurrence in 16 months. 1 died of liver failure 2.5 months later although death was not related to the procedure. 1 patient died of progressive disease 18 months later. The remaining 2 had recurrent tumours 5 and 12 months later, although the treated small tumours showed good response. Histological examination showed cell degeneration and necrosis. It is concluded that laserthermia is potentially useful in the treatment of the patients with small HCC.
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INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is one of the most prevalent malignancies in the orient and sub-Saharan Africa, and the prognosis is poor [1]. With the development of new diagnostic modalities, early detection is now possible [2] and the clinicopathological features are now clearer [3]. For the treatment of HCC, surgical resection is the first choice [4]. For inoperable HCC, transcatheter hepatic arterial embolisation (TAE) has been shown to improve prognosis [4]. However, these treatments are not always satisfactory, and the results of chemotherapy are very poor [5]. Novel modalities of treatments, such as intratumour injection of absolute ethanol [6, 7], OK-432 [8], or interleukin 2 and lymphokine-activated killer cells [9] have also been developed. Although beneficial, there are still drawbacks in these treatments.

Laser therapy has been employed in the treatment of cancer, and laser vaporisation has been used to treat HCC [10]. Laserthermia for metastatic hepatic tumours with frosted laser scalpels has also been reported [11]. However, all of these techniques need laparotomy, and are applicable only to tumours located superficially. For a deeply seated HCC, laser vaporisation or high-power laserthermia with a scalpel is not feasible because of the generation of much heat and gas. By contrast, laserthermia with an interstitial probe and low-power lasers under computer control and thermocouple monitoring does not have such shortcomings [12] and will probably be useful in the treatment of HCC. In recent years, thermal necrosis due to intrahepatic Nd-YAG laser photocoagulation in rats [13] and interstitial laser hyperthermia in the normal canine liver [14] have been studied. Treatment of metastatic cancer of the liver with bare fibres and Nd-YAG lasers under ultrasound guidance has also been reported, with satisfactory results [15]. However, monitoring the temperature in this system is difficult. In the present study, we tried laserthermia in treating small HCC via percutaneous puncture under ultrasound guidance with a newly designed interstitial probe—a hybrid probe which has good laser diffusion and a well controlled temperature monitor. The preliminary results are reported here.

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MATERIALS AND METHODS

Design of the hybrid probe

The newly designed interstitial probe is mainly composed of four parts: the flexible 400 micron quartz fiber for laser conduction, with fibre core 1 cm in length for laser irradiation, laser diffusing material around the fibre core to improve laser diffusion, and a laser transmissive mechanical support tube to