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CLINICAL TRIAL REPORT

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No synergistic activity of epirubicin and interferon-α2b in the treatment of hepatocellular carcinoma

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Abstract Single-agent activity for anthracyclines reflected by response rates of 10%–30% has been reported in patients with advanced hepatocellular carcinoma (HCC). Preclinical data indicate that α-interferon could enhance the cytotoxic activity of the anthracycline Adriamycin or its analog epirubicin. In a phase I/II study, 31 patients with biopsy-proven inoperable HCC were treated with interferon-α2b given s.c. at a dose of 3×10^6 units/m^2 per day for 5 days per week plus weekly epirubicin given at 25 mg/m^2 as an i.v. bolus. The protocol called for 4 consecutive weeks of treatment followed by 1 week off treatment. In all, 15 patients had been previously treated; 6 patients had failed hormonal therapy (tamoxifen), 5 patients had failed prior anthracycline treatment, and 4 patients had received chemoembolization of the tumor and had subsequently progressed. A total of 30 patients were evaluable for response. In all, 1 patient (3%) achieved a partial response for 8+ months and 11 patients (35%) achieved stabilization of disease. Six patients had a fall in alpha-fetoprotein (AFP) values of >50% during therapy. The median survival for all patients was 9.5 months (range, 3–34+ months). The main side effects were hematological toxicity and fever, both of which were considered tolerable. As an indicator of the immunostimulatory effects of interferon, an elevation in serum markers of inflammation [C-reactive protein (CRP), β$_2$-microglobulin] was found in 15%–20% of patients. All patients had measurable Mx protein production during therapy, but these effects were not correlated to the clinical response. The clinical response rate achieved in this trial indicates that the combination of interferon and epirubicin, at least when used on the schedule reported herein, is not superior to treatment with either agent alone for patients with advanced HCC. However, single patients achieved a prolonged progression-free interval (8–10+ months) on this therapy, and it may therefore be an option for patients who have failed prior hormonal or single-agent anthracycline therapy.

Key words Anthracyclines · Epirubicin · Interferon
Hepatocellular carcinoma

Introduction

Although surgical resection is the treatment of choice for patients with hepatocellular carcinoma (HCC), many of them have disease that either is too extensive to permit surgical attack or will reccur shortly after resection. These patients are considered candidates for regional or systemic therapy. Adriamycin has been among the most frequently used drugs for the treatment of HCC, with response rates of 10%–60% being reported in phase II studies [8, 10, 18].

Interferons have a wide range of biological activity, with antineoplastic effects being detected in different tumor models, including a human hepatoma cell line. For interferon-α used as a single agent, response rates ranging between 0 and 41% have been reported in patients with HCC [19]. A recent randomized investigation in Chinese patients has found a significant increase in the duration of survival of patients receiving high doses of interferon in comparison with those receiving no specific antitumor therapy [14]. The explanation for the antitumor effect of interferon is not known. Although interferon does interfere with hepatitis B viral replication in patients with HCC, a direct or indirect immunologically mediated antitumor effect might be more important [15]. Activation of immune parameters, e.g., serum β$_2$-microglobulin levels, has been demonstrated in interferon-treated patients [21].

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Several in vitro studies have documented synergistic activity for combinations of interferon with anthracycline derivates [2, 22, 27]. A schedule dependency of these synergistic effects favoring a prolonged preincubation with interferon prior to anthracycline application has been demonstrated in vitro [23]. In vivo, the synergistic activity of interferon and anthracyclines has been confirmed in different heterotransplanted tumor models, including human breast-cancer xenografts in nude mice, where particularly impressive tumor regressions have been observed [1].

On the basis of these observations, phase I studies combining single doses of Adriamycin with a 5-day schedule of interferon application have been conducted [6, 9, 20]. These studies showed that interferon severely enhanced the myelosuppressive effect of Adriamycin when the anthracycline was given as an i.v. bolus every 3 weeks. One patient with advanced HCC included in these early trials achieved an objective tumor response to this treatment and a fall in α-fetoprotein (AFP) levels from 39,000 to 202 ng/ml [5]. On the basis of these promising observations and the rationale outlined above, weekly i.v. application of epirubicin, an anthracycline derivate with potentially less cardiotoxicity [3], and s.c. administration of interferon-α2b were used to determine the activity of this combination regimen for the treatment of patients with advanced, progressive HCC.

Patients and methods

Clinical studies

A total of 31 patients aged a median of 56 years (range, 21–69 years) who had biopsy-proven inoperable HCC were included in the study. In all, 10 patients had been newly diagnosed and 21 patients had documented tumor progression defined as either an increase of >25% in tumor size as determined in 2 consecutive computerized tomography (CT) scans and/or an increase of >25% in AFP levels at 2 separate evaluations within a 3-month interval. The patients' characteristics, the tumor stage according to the TNM and Okuda classifications [17], and information concerning prior treatment are summarized in Table 1. Nine patients (29%) had had liver biopsies demonstrating cirrhosis prior to the development of HCC. Only patients with measurable disease and/or elevation of AFP serum levels (>10 IU/ml) who were not eligible for surgical resection or other therapy modalities were included. Four patients included in the study were histologically classified as having a fibrolamellar variant of HCC. Pretreatment studies consisted of a medical history, a physical examination, and routine hematological and serum chemistry tests, including determination of AFP levels. Additional requirements were a Karnofsky status of >50%, a WBC of >3,000/μl, a thrombocyte count of >100,000/μl, creatinine clearance of >50 ml/min, adequate liver function (liver enzyme and bilirubin levels of <3 times the upper normal limit), and informed consent.

Treatment was given on an outpatient basis, with interferon-α2b being given s.c. at a dose of 3×10^6 U/m^2 for 5 consecutive days per week and epirubicin being given weekly at 25 mg/m^2 as an i.v. bolus at the 4th day of interferon treatment. The protocol called for 4 weeks of therapy followed by 1 week off treatment. The patients were seen weekly, and the tumor status was assessed every 4 weeks. If toxicity was considered tolerable, the dose of epirubicin was increased in 5-mg/m^2 steps in individual patients. In cases of tumor response and tolerable toxicity, the therapy was continued until disease progression or a maximal tumor response, which was followed by one additional treatment cycle. Response and toxicity were graded according to WHO criteria. No change (stable disease) was defined as a reduction of <50% or an increase of <25% in tumor size and the absence of new metastatic lesions. Time to progression and survival were calculated from the start of treatment.

Table 1 Characterization of patients with HCC

Number of patients	31
Men	20 (65%)
Women	11 (35%)
Median age	56 (range, 21–69) years
Median Karnowsky status	80 (range, 60–90)
Patients with prior cirrhosis of the liver	9 (29%)
Tumor characteristics:	
Okuda stage:	
I	12 (39%)
II	18 (58%)
III	1 (3%)
TNM staging:	
I	0
II	7 (22%)
III	12 (39%)
IVA	9 (29%)
IVB	3 (10%)
Serum AFP levels:	
Normal	6 (19%)
Elevated	25 (81%)
Prior medical therapy:	
None	16 (52%)
Anthracyclines	5 (16%)
Embolization	4 (13%)
Hormone therapy	6 (19%)

Laboratory studies

To evaluate the effects of the low doses of interferon used in the current study on serum parameters of inflammation and on the induction of interferon-responsive proteins, the following parameters were assessed prior to and during therapy with epirubicin and interferon:

1. Serum measurements of C-reactive protein (CRP) and β_2-microglobulin levels as indicators of an inflammatory reaction were performed using commercially available standard immunoassay techniques [CRP, PETIA (particle-enhanced turbidimetric immunoassay); β_2-microglobulin, RIA (radioimmunoassay)] [21].
2. Mx protein levels were determined in mononuclear blood cells (MNC) prior to and during therapy by an enzyme-linked immunosorbent assay (ELISA) as described earlier [26]. Briefly, the MNC were harvested after Ficoll-Hypaque gradient centrifugation (Pharmacia, Freiburg, Germany), and 2×10^6 cells were lysed with 1% sodium dodecyl sulfate (SDS) in phosphate buffer containing 20 n*M* ethylenediaminetetraacetic acid (EDTA). The cellular proteins were precipitated with 96% ethanol, boiled for 2 min, and run on two different SDS-polyacrylamide gels. One gel was stained with Coomassie blue and the other was transferred to nitrocellulose (Biometra, Göttingen, Germany). A monoclonal antibody recognizing the human Mx homolog was applied to nitrocellulose and the reaction was made visible by an alkaline phosphatase – anti-alkaline phosphatase (APAAP) method (Dianova, Hamburg, Germany). The immunoblot was stained with 5-bromo-4-chloro-3-indolyl-phosphate (BCIP) and nitrotetrazolium blue (NBT; both obtained from Sigma, St. Louis, USA). Densitometric readings at 633 nm were performed and adjusted to three internal standards included in the electrophoresis run. The Mx homolog concentration was expressed in laboratory units per milliliter;

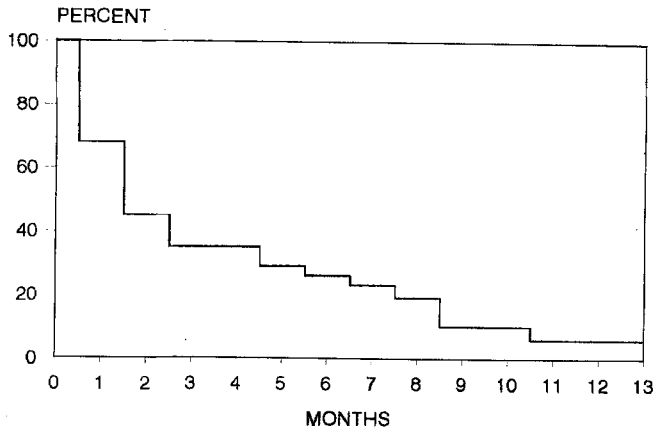

Fig. 1 Time to progression for 31 patients with HCC receiving epirubicin/interferon treatment

1 U Mx homolog/ml is defined as the absorption of a dilution of 1:10 from a WISH cell extract (human amnion cells) from 2×10^6 cells incubated for 24 h with 1,000 IU rh interferon-α2b (rhIFN-α2b)/ml.
3. Serum from all patients was investigated for the development of antibodies against interferon-α2b prior to therapy and at 2–4 months after the start of interferon treatment using a reversed RIA technique (interferon-binding activity) [24]. The interferon-neutralizing activity of patients' sera was determined in a bioassay using the cytopathic effect of vesicular stomatitis virus (VSV) on WISH cells. Serial dilutions of patients' sera were incubated with WISH cells protected against the cytopathic VSV infection by different concentrations of rhIFN-α2b. Depending on the neutralizing capacity of patients' sera for interferon, increased cytopathic effects of VSV on WISH cells were observed [25].

Results

A total of 31 patients were started on epirubicin/interferon treatment between October 1990 and May 1993. A total of 93 cycles of therapy (each lasting 5 weeks), for a median of 3 (range, 1–9) cycles/patient, were applied. Overall, 1 patient (3%) achieved a partial remission lasting for 8+ months with a consecutive fall in AFP levels of >85%, 11 patients (35%) had stabilization of disease, and 18 patients (58%) had disease progression; 1 patient (3%) was not evaluable for response. In all, 3 patients had a reduction of >85% in AFP levels and 3 further patients had a reduction in AFP values of 50%–80% (Table 2).

The median time to progression (Fig. 1) was 3 (range, 1–11+) months for all patients and 6 (range, 2–11+) months for patients achieving stable disease. The median duration of survival was 9.5 (range, 3–34+) months. In all, 4 of 5 patients who had experienced documented progression during or relapse after prior anthracycline treatment achieved stabilization of disease. No correlation was found between the tumor stage and the response to therapy.

Escalation of the epirubicin dose to a maximum of 35 mg/m² weekly was possible in 4 patients. In 3 patients the dose of epirubicin was reduced by 5 mg/m² due to hematological toxicity. The toxicity encountered according to WHO classification is summarized in Table 3. Grade III/IV leukopenia occurred in 45% of patients and grade III thrombocytopenia, in 6%. In all, 2 patients developed infections during neutropenia, and 14 patients (45%) experienced myalgia, fever, and lethargy with a decreasing frequency during the consecutive cycles of treatment. No clinical sign of congestive heart failure was observed. No unexpected enhancement of epirubicin toxicity by coadministration of interferon was observed.

Serum for the measurement of inflammation markers prior to and during therapy was available from 20 patients. Increased levels of CRP (>0.5 mg/dl) during therapy without signs of infection and with normal pretreatment levels were found in 4 patients (20%; range, 3.2–9 mg/dl). An increase in β_2-microglobulin levels (>2.5 mg/dl) during therapy was found in 3 patients (15%; range, 2.8–4.1 mg/dl). Mx protein production was determined in 12 patients prior to therapy and in 20 patients at least once during therapy (after 2–4 months). All 12 of the former patients were negative for Mx protein production (defined as <0.02 U/ml) prior to therapy, and in all 20 of the latter patients, measurable levels of Mx homolog ranging from 0.023 to 1.38 U/ml (mean, 0.313 U/ml) were found during therapy, indicating that the dose of interferon used had resulted in the activation of gene transcription in mononuclear cells. In 5 patients in whom Mx homolog was measured at >6 weeks after the end of therapy, a mean of 0.022 U/ml (range, 0.0–0.06 U/ml) was determined. In the 30 patients tested, no antibody to interferon-α2b had developed during therapy and no interferon-neutralizing activity was found. Furthermore, no preexisting antibody against interferon was detected prior to therapy.

Table 2 Response to therapy with weekly epirubicin and daily interferon-α2b in 30 patients with progressive HCC[a]

Response	Number of patients
CR	0
PR	1/30 (3%)
SD	11/30 (37%)
PD	18/30 (60%)
Reduction in AFP levels >50% of initial value	6/30 (20%)

[a] 1 patient was not evaluable due to nonmeasurable disease

Table 3 Side effects of treatment with epirubicin/interferon-α2b in 31 patients with progressive HCC. Values are given as the worst toxicity per patient

	WHO grade		
Toxicity	II	III	IV
Leukocytopenia	11 (35%)	12 (39%)	2 (6%)
Thrombocytopenia	3 (10%)	2 (6%)	–
Anemia	8 (26%)	5 (16%)	2 (6%)
Nausea/vomiting	3 (10%)	1 (3%)	–
Diarrhea	2 (6%)	1 (3%)	1 (3%)
Mucositis	2 (6%)	2 (6%)	–
Fever	12 (39%)	–	–

Discussion

The low cure rate of HCC by surgery alone demonstrates the need for effective nonsurgical treatment. Epirubicin and α-interferon used as single agents have demonstrated activity in HCC. Preclinical and in vivo tumor models have indicated a possibly synergistic activity for their combination [22, 23]. However, the results obtained in 31 patients with HCC in the current study demonstrate that the combination of epirubicin and interferon given on the schedule used did not achieve the favorable results reported in previous phase I studies, with 1 of 8 patients achieving a partial response (PR) in 1 study and 3 of 17 HCC patients achieving a PR in another phase II trial [6, 16, 20]. Although the median survival of 9 months obtained in the current study, may compare favorably with other series reported in the literature [4], this may also be explained by the observation that only one-third of the patients included in the current trial had biopsy-proven concomitant liver cirrhosis.

The schedule used in this phase I/II study was based on in vitro results indicating that low doses of interferon such as those used by us are sufficient to influence effectively anthracycline drug activity [1, 25]. Weekly treatment with epirubicin was chosen to avoid the high degree of myelotoxicity associated with 3-week administration of standard-dose Adriamycin therapy. In our study, no significant increase in epirubicin toxicity was seen following the coadministration of low doses of interferon. Escalations of the epirubicin dose to >35 mg/m^2 were not possible due to hematological side effects. Although patients reported the treatment to be generally well tolerable, 45% of them experienced fever after interferon administration and 1 patient stopped receiving interferon due to an interferon-related wasting syndrome.

The activation of serum parameters of inflammation such as CRP and β_2-microglobulin without clinical signs of infection was found in 20% and 15% of patients, respectively. In the mononuclear cells of 20 patients available for the analysis of Mx protein, a 78-kDa protein used as a parameter for the gene transcriptional activity of interferons [26], positive reactions (0.02–1.38 U/ml) were found in all cases. Although this confirms the activity of the rather low doses of interferon used in the current trial, there was no correlation between the expression of either Mx protein or serum markers of inflammation and the clinical response. On the other hand, the two patients with the highest Mx protein levels also did not experience more severe side effects. In a trial of interferon and vinblastine therapy in patients with metastatic melanoma, even depression of immunological parameters was found in patients with progressive disease [12]. This might indicate that concurrent chemotherapy – at least that with vinblastine in the above-mentioned study – may counteract the immunostimulatory effects of interferon. However, the role of immune stimulation by interferons in general as part of the treatment of patients with solid tumors has not yet been clearly demonstrated. The low antitumor activity found for the combination of epirubicin and interferon in our trial was not related to the neutralization of interferon activity by specific antibodies, because none of the patients had developed antibodies to interferon [25].

Single-agent interferon or anthracycline treatment should be regarded as standard therapy for advanced HCC. In a randomized trial in China comparing interferon with an anthracycline, interferon-α was associated with a higher response rate and less severe side effects and, thus, might even be preferable to Adriamycin [13]. However, this was a rather small study and high doses of interferon were used. In another trial, also performed in Chinese patients, high-dose interferon treatment (50×10^6 IU/m^2 given three times per week) resulted in a significant prolongation of survival as compared with no antitumor treatment [14]. However, there may be considerable ethnic differences between HCC patients from China and those from Europe, making the comparison of treatment results difficult.

The explanation for the low clinical synergistic activity observed for the combination regimen in our patients remains unclear. It has previously been demonstrated that α-interferon does not influence the pharmacokinetics of epirubicin [7]. Since the response rates observed in the current trial do appear to be even lower than those obtained with standard-dose 3-week Adriamycin therapy, the question arises as to whether the use of a weekly epirubicin schedule might in part have been responsible for the poor results achieved. On the other hand, the dose of interferon used might have been too low to exert a significant antitumor effect on its own.

A 5-day schedule of interferon application surrounding the administration of epirubicin may not have been the optimal schedule for the treatment of these patients. However, results similar to those obtained by our group have been reported in a phase II trial of 31 patients with HCC using a combination of 12×10^6 U/m^2 interferon-α given for 5 days with the weekly administration of 25–40 mg/m^2 Adriamycin [11]. Only one objective tumor response was observed in this trial, but the hematotoxicity, fever, and myalgia encountered were more severe than those observed in our study, indicating that the use of a high-dose interferon regimen may be associated not with better treatment results but with more toxicity.

The addition of low-dose interferon to epirubicin therapy did not significantly enhance the clinical activity of the anthracycline derivative. Furthermore, despite the immunological activity demonstrated, no clinical efficacy of interferon was observed in our patients with HCC. Although two patients in our series showed long-term responses to therapy, it is reasonable to conclude that the combination of α-interferon and epirubicin, according to the schedule used, does not lead to a substantial improvement in the treatment of patients with HCC.

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