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Short Communication

Phase I Study of a Weekly 1 h Infusion of Paclitaxel in Patients with Unresectable Hepatocellular Carcinoma

D. Strumberg,[1] J. Erhard,[2] A. Harstrick,[1] U. Klaassen,[1] C. Müller,[1] W. Eberhardt,[1] H. Wilke[1] and S. Seeber[1]

[1]Department of Internal Medicine (Cancer Research), West German Cancer Centre; and [2]Department of Surgery, University of Essen, Hufelandstraβe 55, 45122 Essen, Germany

The majority of patients with hepatocellular carcinoma will develop either unresectable or metastatic disease and, therefore, are candidates for systemic chemotherapy. Only a few chemotherapeutic agents have shown documented activity in the treatment of advanced hepatocellular carcinoma and there is clearly a need for the evaluation of new active drugs. Therefore, we performed a phase I trial with a weekly schedule of paclitaxel in patents with advanced hepatocellular carcinoma. 16 patients with documented progression of unresectable hepatocellular carcinoma were included. After premedication, paclitaxel was given as a 1 h infusion on days 1, 8, 15, 22, 29 and 36 representing one treatment cycle. The cycle was repeated every 50 days. The starting dose was 70 mg/m^2 and the doses were escalated in steps of 10 mg/m^2/week. A minimum of 3 patients were treated at each dose level. All treatment was given on an out-patient basis. Dose-limiting toxicity was reached at a dose of 100 mg/m^2/week with 2 of 6 patients treated at that dose level having WHO grade 4 neutropenia. Other toxic side-effects were only mild. 1 partial response and 9 cases with disease stabilisation were observed in 16 patients with initially progressive disease. We, therefore, conclude that the recommended dose for a further phase II trial in patients with hepatocellular carcinoma is 90 mg/m^2/week. These data indicate that paclitaxel given at this dose and schedule might have activity in hepatocellular carcinoma and further investigation in phase II trials is warranted. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is one of the most common malignancies, causing an estimated 1.2 million deaths every year world-wide. It is almost always associated with chronic liver disease, mainly hepatitis B and hepatitis C. Less than 30% of patients with HCC are considered as candidates for curative resection and even in this favourable subgroup, long-term survival is less than 15%. Because of the course of the disease, the majority of patients are potential candidates for chemotherapy, used either as palliative treatment or peri-operatively. Combination chemotherapy does not appear to be superior to doxorubicin alone which can induce an objective response rate of 20% and median survival times of approximately 6 months in selected patients [1]. Therefore, there is an urgent need for new and active drugs for the systemic treatment of HCC.

Paclitaxel is a novel cytotoxic agent with significant clinical activity in a considerable number of solid tumours. In most anthracycline-sensitive tumours, paclitaxel has been at least as active as the anthracyclines and has induced remissions even in anthracycline-resistant disease. Moreover, paclitaxel has demonstrated activity in tumour entities such as non-small cell lung cancer, head and neck cancer and oesophageal cancer, where anthracyclines are not regarded as active [2].

Based on these experiences, the investigation of paclitaxel in HCC appears to be meaningful. Considering the cellular mode of action of paclitaxel, which is predominantly

Correspondence to D. Strumberg.
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cytotoxic for dividing cells, frequently repeated doses in a weekly schedule could offer an advantage over application every 3–4 weeks [3, 4]. Paclitaxel, given in a weekly 1 h infusion, was safe and showed mild toxicity in heavily pretreated breast and ovarian cancer patients in a previously published phase I trial [5]. The recommended dose in that study was 90 mg/m^2/week. This was the background for the current phase I trial with a weekly schedule of paclitaxel in patients with unresectable HCC.

PATIENTS AND METHODS

Inclusion criteria

Patients in this study had histological proof of advanced hepatocellular carcinoma, not amenable to surgery. All patients had to have progressive bidimensionally measurable lesions and were chemotherapy naive. Other inclusion criteria were: age < 75 years, WHO performance status < 3, life expectancy of > 3 months, adequate renal, liver (total bilirubin and serum creatinine levels were required to be ≤ 1.5 times the upper normal limit) and bone marrow function (ANC $\geq 3000/\mu l$, thrombocytes $\geq 100\,000/nl$). All patients gave their informed consent. The study was approved by the local ethics committee.

Staging and follow-up

Prior to treatment, all patients underwent complete medical history, physical and neurological examination, electrocardiogram, chest X-ray, computer tomography (CT) scan and ultrasound. During treatment, patients had weekly full haematological blood counts, determination of liver and renal functions and assessment of non-haematological toxicities. In addition, AFP measurements were performed at study entry and during the follow-up. Response to treatment was assessed prior to each cycle. The standard WHO criteria [6, 7] were used for evaluation of toxicities and response.

Treatment schedule

Paclitaxel was given as a 1 h infusion on days 1, 8, 15, 22, 29 and 36 representing one treatment cycle. The cycle was repeated every 50 days. All patients were treated as outpatients. The premedication consisted of dexamethasone (8 mg oral 12 and 6 h prior to each paclitaxel infusion) and cimetidine (400 mg intravenously) and clemastine (2 mg intravenously) 30 min before each infusion of paclitaxel.

Dose escalation

The following dose levels were chosen: dose level 1 (starting dose), 70 mg/m^2/week; dose level 2, 80 mg/m^2/week; dose level 3, 90 mg/m^2/week; dose level 4, 100 mg/m^2/week. No dose escalation was allowed in individual patients. Paclitaxel was administered if no dose-limiting toxicity (DLT) was present on the day of treatment. DLT was defined as: neutropenia grade 4, anaemia and thrombopenia > grade 2, other organ toxicity > grade 2 according to WHO criteria [6, 7] with the exception of alopecia. If a patient did not fulfil these criteria, the day of the planned application of paclitaxel was postponed until all side-effects had resolved and then continued using the next lower dose level. A minimum of 3 patients were treated at each dose level. If no DLT occurred, 3 patients entered the next dose level. If 1 of 3 patients at a given dose level experienced DLT, 3 additional patients had to be entered. The maximum tolerated dose (MTD) was reached if DLT occurred in 2 or more of 6 patients at one dose level.

RESULTS

16 patients were included in the study. The median age was 60 years (range 42–72 years; m/f = 11/5 patients), the median performance status according to WHO criteria was 1 (range 0–2). All patients had bidimensionally measurable disease and documented progression prior to inclusion in the study; 3 patients presented with additional extrahepatic metastasis (bone, peritoneum, lung). 11 patients had liver cirrhosis (all Child A according to Child–Pugh criteria), 3 of the 16 patients presented a positive hepatitis B_S-antigen status. No patient required palliative billiary derivation prior to study entry. 3 patients had Okuda-stage I and 13 patients had Okuda-stage II. No DLT was seen in 10 patients treated at dose level 1 (3 patients, 40 single weekly doses (SWD)), dose level 2 (3 patients, 49 SWD) and dose level 3 (4 patients, 53 SWD), respectively (Table 1). At dose level 4 (100 mg/m^2/week), 2 of 6 patients experienced DLT. 1 patient developed grade 4 neutropenia after the second SWD and the other patient suffered from grade 4 neutropenia after the fifth SWD of paclitaxel. In both cases, neither hospitalisation nor antibiotic therapy were necessary. Treatment in those patients was postponed until full recovery from side-effects and then continued using the next lower dose level. According to protocol guidelines, MTD was reached using dose level 4. The

Table 1. *Frequency of toxicities* (n) *in single weekly doses (SWD) per dose level*

	Dose levels							
	1 ($n = 3$, 40 SWD)		2 ($n = 3$, 49 SWD)		3 ($n = 4$, 53 SWD)		4 ($n = 6$, 40 SWD)	
WHO grade	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4
Neutropenia	–	–	–	–	3	1 (grade 3)	3	2 (grade 4)
Anaemia	–	–	–	–	2	–	–	–
Thrombopenia	–	–	–	–	–	–	–	–
Nausea/vomiting	–	–	1	–	–	–	1	–
Myalgia	–	–	–	–	–	–	1	–
PNP	–	–	1	–	3	–	2	–
Diarrhoea	–	–	–	–	1	–	2	–
Mucositis	–	–	–	–	1	–	1	–
HSR	–	–	–	–	–	–	–	–

PNP, peripheral neuropathy; HSR, hypersensitivity reaction.

Table 2. Dose intensity and response to treatment

Dose level	Dose (mg/m^2/week)	*n*	SWD (*n*)	Treatment delay (weeks)	Dose intensity (mg/m^2/week)	Response	Time to progression (weeks) (range)
1	70	3	40	–	70	PD1, SD2	21 (13–28)
2	80	3	49	1	80	PD1, SD1, PR1	24 (20–28)
3	90	4	53	4	83	SD4	27 (8–44)
4	100	6	40	7	86	PD4, SD2	18 (12–24)

SWD, single weekly doses; PD, progressive disease; SD, stable disease; PR, partial remission.

patients with grade 1 and grade 2 peripheral neuropathy [6, 7] had prior liver cirrhosis. However, there was no relationship between the cumulative paclitaxel dose and the peripheral neuropathy grade. Using the premedication programme as detailed in the protocol, no hypersensitivity reactions occurred in dose levels 1–4. Furthermore, only 1 patient suffered from moderate corticosteroid induced side-effects; further premedication with 50% of the corticosteroid dose in this patient was well tolerated. All patients had documented progression of their disease according to WHO criteria prior to study entry. 1 patient at dose level 2 had a partial remission and 9 patients had stable disease according to WHO criteria. The median time to progression was 22 weeks with a range of 8–44 weeks (Table 2). 10 of 16 patients had pathological AFP values at study entry. The patient with an objective partial remission according to WHO criteria [6, 7] had a decreased AFP level (from 2,359 to 600 U/ml). 2 additional patients at dose level 2 and 3, respectively, presented a decrease in their AFP level (from 3,160 to 387 U/ml and from 29 000 to 4,070 U/ml, respectively), whereas the objective tumour parameter reflected a stable disease. An improvement of tumour-related symptoms (pain, weight loss, dyspnoea) was seen in the patient with a partial tumour remission and in 6 of 9 patients with stable disease.

DISCUSSION

The majority of patients with hepatocellular carcinoma will develop either locally unresectable or metastatic disease. Therefore, most patients will benefit from effective systemic chemotherapy. At present, only very few agents have shown documented activity in the range of 10–20% objective remissions. These include the anthracyclines doxorubicin and 4-epidoxorubicin [8], mitoxantrone [9] and possibly interferon-alpha when given at very high-doses [10]. Responses to these agents are usually short lived and there is a clear need for the evaluation of new, active drugs.

Paclitaxel has shown activity in a variety of malignant diseases, most notably in breast and ovarian cancer and in non-small cell lung cancer when given at a dose of 135–175 mg/m^2 every 3 weeks [2]. Since the drug is cell cycle specific and preferentially acts on cells in the late G2 and M phase, more frequent application might result in increased antitumour activity [3, 4]. In a previous phase I trial in patients with advanced ovarian and breast cancer, we demonstrated that paclitaxel can be given weekly, even in these heavily pretreated patients [5]. The MTD reached in this patient population was 100 mg/m^2/week with reversible leucopenia being the main side-effect. Since that study population consisted of heavily pretreated patients, we decided to perform a second phase I trial in patients with advanced hepatocellular carcinoma, who were chemotherapy naïve. In this phase I trial, the MTD was reached at 100 mg/m^2/week and neutropenia was found to be the DLT. At dose level 3, however, the treatment was associated with mild to moderate toxicities when paclitaxel was given at a dose of 90 mg/m^2/week. This is also the dose which is recommended for a phase II trial. The dose intensity of paclitaxel achieved with this weekly administration was 83 mg/m^2/week.

Although this was a phase I trial and antitumour activity was not the primary endpoint, we observed activity of paclitaxel in patients with hepatocellular carcinoma. With documented tumour progression prior to study entry, 1 of our 16 patients achieved a partial remission according to WHO criteria and an additional 9 patients had prolonged stable disease. Furthermore, most patients with stable disease experienced an improvement in tumour-related symptoms. Therefore, it is justified to evaluate further the efficiency of paclitaxel given as a weekly infusion in patients with advanced hepatocellular carcinoma in a formal phase II trial.

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