Cancer Chemother Pharmacol (1999) 44: 307–311

ORIGINAL ARTICLE

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A multi-centre randomized phase II study of nolatrexed versus doxorubicin in treatment of Chinese patients with advanced hepatocellular carcinoma

Received: 26 October 1998 / Accepted: 20 January 1999

Abstract *Purpose*: A multi-centre randomized phase II study of single agent nolatrexed dihydrochloride versus doxorubicin was undertaken in Chinese patients with advanced hepatocellular carcinoma (HCC) to study and compare the clinical efficacy of the two drugs. *Methods*: Fifty-four patients with clinical or histological diagnosis of HCC were randomized in a 2:1 ratio to receive nolatrexed or doxorubicin. Nolatrexed 725 mg/m^2/day was given by continuous infusion via a central venous device for 5 days and doxorubicin 60 mg/m^2 was given as a rapid intravenous infusion every 3 weeks. *Results*: No objective responses were observed in either treatment arm. Two patients in the nolatrexed arm and none in the doxorubicin arm had $>50\%$ decline in serum α-fetoprotein. The median survival for the patients in the nolatrexed and doxorubicin arms was 139 days and 104 days, respectively. Moderate toxicities including leukopenia, thrombocytopenia, mucositis and skin rash were observed in both treatment arms. *Conclusion*: Nolatrexed and doxorubicin are minimally active in the treatment of advanced HCC. Given the small sample size, no difference is observed between the two drugs.

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Key words Hepatocellular carcinoma · Nolatrexed · Doxorubicin · Randomized study

Introduction

Unresectable hepatocellular carcinoma (HCC) remains one of the most rapidly fatal malignant diseases with little hope of cure or prolonged survival. Patients with good performance status and adequate liver function are treated with locoregional therapy such as trans-arterial chemo-embolization or selective internal radiation [2, 13]. In spite of improvement in the response rates by these treatments, survival benefit has not been proven. Systemic chemotherapy and supportive care are the only options for patients who are not eligible for locoregional treatment. However the results of single agent and combination chemotherapy have been disappointing [14]. The response rates of most treatment protocols including single agent doxorubicin were less than 20% with median survival in terms of weeks. Nonetheless single agent doxorubicin has remained the standard systemic treatment against which new modalities are compared [17]. In this randomized phase II trial we have studied the clinical efficacy of nolatrexed, a novel thymidylate synthase (TS) (15) inhibitor and attempted to compare its activity to single agent doxorubicin.

Nolatrexed (Thymitaq AG337) is a novel TS inhibitor designed according to the x-ray crystallography of the three dimensional structure of TS [9, 24]. Nolatrexed binds at the co-factor binding site of TS, thus retarding the biosynthesis of thymidylate. The drug is lipophilic, thus facilitating non-specific cellular uptake and improvement in drug exposure to the tumour cell [25]. Phase I clinical studies have confirmed that 5 days administration of nolatrexed is safe [19, 20] and that the drug is cytotoxic against a variety of solid tumours. The efficacy in treatment of head and neck squamous cell carcinoma and HCC appeared to be most promising. The response rate was 22% for the 27 evaluable patients with head and neck squamous cell carcinoma [5]. Stuart

et al. reported, in a phase II study on 27 patients with advanced HCC, that two patients attained partial response lasting at least 6 months and two had >50% decline in α-fetoprotein (AFP) [22]. We designed this randomized phase II trial to study the clinical efficacy of continuous infusion of single agent nolatrexed versus standard bolus infusion of doxorubicin in treatment of patients with advanced unresectable HCC. We intended to increase sample size of the study if promising response rates were observed with the nolatrexed treatment.

Patients and methods

Patients

This multi-centre study enrolled patients from institutes in Hong Kong, Taiwan (two sites) and Singapore. Patients with unresectable or metastatic HCC were randomized in a ratio of 2:1 to receive nolatrexed or doxorubicin, respectively. The diagnosis of HCC was confirmed either by histology or radiological evidence of hepatic mass with a serum AFP of 500 ng/ml or more. Other inclusion criteria were: age ≥18 years, measurable disease, Karnofsky performance score ≥70, neutrophil count ≥1500/mm^3, platelet count ≥75 000/mm^3 and informed consent. Patients with poor liver function (bilirubin >3 mg/dL, AST or ALT >5.0 × upper normal limit or albumin <3 g/dL) were excluded. Other exclusion criteria were: ascites not manageable by medication alone, prior chemotherapy within 4 weeks, prior abdominal surgery within 4 weeks, other malignancy within the past 5 years or concurrent severe medical conditions. For patients who were randomized to the doxorubicin arm, an echocardiogram was performed to ensure a left ventricular ejection fraction of 60% or more.

Treatment plan

Nolatrexed was administered via a central venous device (Hickman line or Peripherally Inserted Central Catheter) to avoid local irritation to the peripheral vein. Nolatrexed (725 mg/m^2) was dissolved in 50 ml of normal saline and infused continuously by the CADD (Continuous Administration of Drug Device) pump over 24 h daily for 5 days every 3 weeks. Doxorubicin (60 mg/m^2) was administered as a short intravenous bolus once every 3 weeks. Dose modification for subsequent cycles of nolatrexed was made according to the severity of maximum toxicities observed in the previous cycle (Table 1). These toxicities were graded according to the World Health Organization (WHO) recommendation for toxicity grading. Patients receiving doxorubicin would have dose reductions on subsequent cycles of 25% and 50% for grade 3 and grade 4 toxicity, respectively.

Disease evaluation, response and survival

All patients had a complete medical history and physical examination at enrolment. Standard blood tests included complete blood count, renal function tests, serum AFP, liver function tests and hepatitis B serology. Bi-dimensional measurements (tumour size was measured as the product of the maximum perpendicular diameters) were made within 4 weeks of randomization by abdominal ultrasound or computerized axial tomography. With each cycle of chemotherapy, the physical examination and blood tests including AFP were monitored. The measurable lesion(s) was (were) evaluated every 6 weeks (or two cycles) with the same diagnostic imaging technique as the pre-treatment measurement. Patients were considered to have complete response (CR) if all measurable and evaluable disease disappeared completely. Partial response (PR) was defined as ≥50% decrease from baseline in the sum of products of perpendicular diameters of all measurable diseases. The decrease had to be durable over two evaluations of at least 4 weeks apart. Disease was classified as progressive (PD) if a ≥50% increase in the sum of products of perpendicular diameters of all measurable diseases was observed. Stable disease (SD) was diagnosed in patients not qualifying for CR, PR or PD. Progression-free survival was defined as the number of days from the date of randomization until first documentation of progression or death. Overall survival was measured from the date of randomization to the date of last event or death.

Table 1 Nolatrexed dose modification. *WHO* World Health Organization

Toxicity (WHO)	Subsequent dose (increase/decrease from previous dose)
Grade 0	Increase 25%
Grade 1	Increase 15%
Grade 2	No change
Grade 3	Decrease 15%
Grade 4	Decrease 25%

Statistical methods

This study was designed as a phase II/III randomized control trial. The phase II study sample size was calculated according to Simon's minimax design. Assuming a lower response rate of 5% and higher response rate of 20%, 29 evaluable patients were required in the nolatrexed arm at stage one. If two or more patients in the nolatrexed arm had PR or CR, the study would proceed to stage two with target accrual at 38 patients in total. This would give a power of 0.90 with the drug having a true response rate of 20%. If results of the two stages of the study indicated a favourable response, the study would continue to the full population of 200 patients (133 patients in the nolatrexed arm and 67 in the doxorubicin arm). The third stage was designed with an alpha value of 0.05 and a power of 0.80 for 17.5% difference in objective response rate. Secondary endpoints including progression-free survival and overall survival were calculated by the Kaplan-Meier method.

Results

Patient characteristics

Between August 1996 and December 1997, 54 patients were enrolled to the study. The patient characteristics are summarized in Table 2. All patients were ethnic Chinese. They were predominately middle-aged male hepatitis B carriers (78%) with cirrhosis (59.2%) and good performance status (mean Karnofsky performance score = 90). About half of the patients (51.8%) had histological confirmation of HCC. The tumours were generally large (mean tumour size = 120.3 cm^2) and limited to liver (66.7%). Nine patients received single agent cisplatin as prior treatment by chemoembolization, intra-arterial or systemic chemotherapy.

Treatment

Six patients dropped out of the study protocol after randomization: two in the nolatrexed arm and four in the doxorubicin arm. The main reason for withdrawal was refusal of the assigned treatment. A total of 103

Table 2 Patient characteristics. *AFP* α-fetoprotein

	Nolatrexed arm [n = 37 (%)]	Doxorubicin arm [n = 17 (%)]	Total [n = 54 (%)]
Age			
Mean	55.7	51.4	54.3
Range	30.9–74.2	30.9–64.7	30.9–74.2
Sex			
Male	37 (100)	12 (70.6)	49 (90.7)
Female	0 (0)	5 (29.4)	5 (7.4)
Diagnosis by			
Histology	17 (45.9)	11 (64.7)	28 (51.9)
Radiology + AFP >500 mg/ml	20 (54.1)	6 (35.3)	26 (48.1)
Stage			
Limited to liver	28 (75.7)	8 (47.1)	36 (66.7)
Distant metastasis	9 (24.3)	8 (47.1)	17 (31.5)
Risk factors			
Hepatitis carrier	28 (75.7)	14 (82.4)	42 (77.8)
Hepatitis C positive	2 (5.4)	1 (5.9)	3 (5.6)
Alcohol abuse	4 (18.8)	0 (0)	4 (7.4)
None	3 (8.1)	2 (11.7)	5 (9.2)
Hepatic cirrhosis			
Present	22 (59.5)	10 (58.8)	32 (59.3)
Unknown	15 (40.5)	7 (41.2)	22 (40.7)
Portal vein invasion			
Present	19 (51.4)	7 (41.2)	26 (48.1)
Absent	18 (48.6)	10 (58.8)	28 (51.9)
Prior treatment			
None	29 (78.4)	12 (70.6)	41 (76)
Surgery	4 (10.8)	5 (29.4)	9 (16.7)
Chemoembolization	5 (13.5)	1 (5.9)	6 (11.1)
Intra-arterial chemotherapy	0 (0)	2 (11.8)	2 (3.7)
Radiotherapy	0 (0)	1 (5.9)	1 (1.9)
Systemic chemotherapy	1 (2.7)	0 (0)	1 (1.9)
Other	0 (0)	1 (5.9)	1 (1.9)

courses of nolatrexed were delivered to 35 patients compared with the total of 36 courses of doxorubicin given to 13 patients. In the nolatrexed arm, six and seven patients had dose reduction and escalation, respectively. Two patients in the doxorubicin arm had dose reduction as result of myelosuppression. Twenty-six per cent and 38.5% of patients in the nolatrexed and doxorubicin arm were able to complete three or more courses of treatment, respectively. The most common reason for treatment cessation in both arms was disease progression.

Toxicity

Treatment toxicities of the 35 patients in the nolatrexed arm and 13 patients in the doxorubicin arm are summarized in Table 3. Myelosuppression was significant in both groups of patients. One patient in the nolatrexed arm died from neutropenic sepsis. No patient had major haemorrhage as result of thrombocytopenia. Severe non-haematological toxicity was more common in the nolatrexed arm. Twenty per cent of patients reported severe (WHO grade 3 or 4) stomatitis, which required rigorous therapy including sodium bicarbonate mouthwash and nystatin mouthwash and intravenous hydration. Despite routine antihistamine therapy, skin rashes were common, but mild, in the nolatrexed arm.

Response and survival

In addition to the six patients who refused treatment after randomization, three patients in the nolatrexed arm and one patient in the doxorubicin arm were not evaluable because they lacked the post-baseline disease assessment. Among the 32 evaluable patients in the nolatrexed arm there was no CR or PR. Seven patients had SD (21.8%) and 23 (71.8%) patients had PD. Almost all progression of disease was noted within the first three courses of treatment. The response rate of patients in the doxorubicin arm was similar. Among the 12 evaluable patients there was no CR or PR, two SD

Table 3 Toxicities

	Number of patients (%) ≥ Grade 3 toxicity	
	Nolatrexed arm (n = 35)	Doxorubicin arm (n = 13)
Leucopenia	8 (22.9)	4 (30.7)
Neutropenia	9 (25.7)	9 (69.2)
Thrombocytopenia	3 (8.6)	0
Anaemia	4 (11.4)	1 (7.7)
Nausea	1 (2.9)	0
Anorexia	1 (2.9)	0
Stomatitis	7 (20)	1 (7.7)
Skin rash	1 (2.9)	0
Alopecia	0	1 (7.7)
Vomiting	4 (11.4)	0

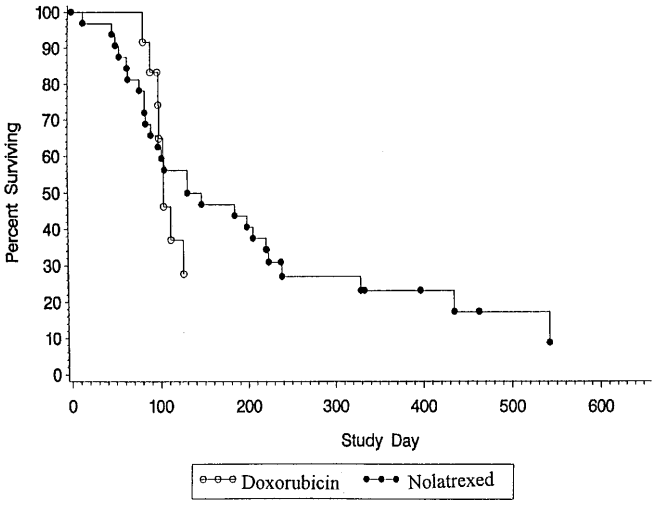

Fig. 1 Overall survival curves for the doxorubicin and nolatrexed arms

(16.7%) and nine PD (75%). Two nolatrexed-treated patients had ≥50% decrease in serum AFP and SD. One patient completed 17 courses of nolatrexed and survived for 23 months, and the other completed 14 courses and survived for 17 months. The median survival of patients in the nolatrexed and doxorubicin arms was 139 days and 104 days, respectively ($P = 0.9843$). The progression-free survival was 48 days and 47 days, respectively. The Kaplan-Meier curves for overall survival are shown in Fig. 1.

Discussion

This study shows that nolatrexed has minimal activity in treatment of advanced HCC. No objective response was observed among the 35 patients who received nolatrexed and the study was subsequently terminated. The low response rate may, in part, be due to the fact that some patients had previously received and failed on other forms of chemotherapy. Only two other studies of nolatrexed in the treatment of HCC have been conducted. The first study [22] involved 26 patients with advanced HCC. Two patients experienced objective response and three patients had >50% decline in AFP. The median survival was 179 days for the intention-to-treat group. The other was a single-arm study [1] conducted in North America with treatment protocol similar to our study. One of the 40 evaluable patients had PR and two patients had ≥50% decline in AFP. The median survival was 183 days. These results are entirely consistent with the present study.

The outcome of doxorubicin-treated patients in this study is disappointing. The response rate is zero and median survival is only 104 days. This finding is worse than that reported in the literature, although it should be noted that our sample size was small. Among all the available cytotoxic agents for treatment of advanced HCC, doxorubicin has been considered to be the most effective single agent. Table 4 summarizes the response rates and median survival reported in early phase II studies of single agent doxorubicin [3, 4, 6–8, 10–12, 15, 16, 18, 21, 23]. The response rates of these phase II studies range from 9% to 44%. The median survival of 13–18 weeks is similar to the survival of patients in the doxorubicin arm of our study. In a randomized phase II study Lai et al. [12] treated 60 patients with doxorubicin and compared them with 46 patients given best supportive care alone. Only two patients (3.3%) in the doxorubicin arm responded. The median survival was similar. He concluded that doxorubicin did not improve duration of survival in patients with advanced HCC.

We had initially intended to compare the clinical efficacy of nolatrexed and doxorubicin. However, the study was terminated due to lack of response in the first 29 patients and the decision of the pharmaceutical company to stop all further development of this drug. Limited by the small sample size, comparison of the two treatments is not valid, although it is interesting to observe that there is a 41% difference between the median survivals in the two treatment groups.

In this multi-centre randomized phase II study, we show that both nolatrexed and doxorubicin have minimal cytotoxic activity as single-agent treatment in advanced HCC. Doxorubicin, despite its general usage in HCC, has not been shown to be efficacious in the Chinese population with predominantly hepatitis B-related

Table 4 Phase II studies of single agent doxorubicin in treatment of hepatocellular carcinoma. *NA* not available

Author	Dosage (mg/m^2)	Response rate (%)	Median survival (weeks)
Olweny et al. [18]	35–75	22/50 (44)	NA
Chlebowshi et al. [3]	75	6/52 (11)	NA
Choi et al. [4]	70	11/45 (24)	14.4
Falkson et al. [7]	40–60	3/34 (9)	12
Ihde et al. [8]	60–75	2/13 (15)	13
Vogel et al. [23]	20–75	4/22 (18)	NA
Colombo et al. [6]	60	7/28 (25)	18
Johnson et al. [10]	60	14/44 (32)	14
Kalayci et al. [11]	60	3/22 (14)	17
Melia et al. [15]	60	5/21 (24)	16
Sciarrino et al. [21]	60	11/109 (10)	NA
Melia et al. [16]	60	3/28 (11)	9
Lai et al. [12]	60–75	2/60 (3.3)	10.6

HCC. We recommend that Chinese patients with advanced HCC, who are eligible for systemic chemotherapy, should be enrolled in clinical study in search of better treatment.

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