Phase II Study of Flutamide in the Treatment of Hepatocellular Carcinoma

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BACKGROUND. Hepatocellular carcinoma (HCC) is a male predominant disease and may be an androgen-dependent or androgen-responsive tumor. This Phase II study was designed to investigate the clinical activity and toxicity of flutamide in the treatment of patients with advanced HCC.

METHODS. Thirty-two patients with measurable advanced HCC were studied. Flutamide, 750 mg per day, was administered orally for 8 weeks. Ten patients died before repeat tumor measurements could be performed.

RESULTS. Twenty-two patients were evaluable for response and toxicities. There were no complete responses nor partial responses. Nine of 22 patients (41%) had stable disease and 13 patients (59%) had progressive disease. Serum alpha-fetoprotein was reduced in three patients. The median survival was 10 weeks (range, one to 35 weeks). Toxicities were minimal and tolerable.

CONCLUSIONS. Flutamide is not effective in the treatment of advanced HCC. Clinically, HCC may not be an androgen-responsive tumor. Other new methods of treatment of HCC warrants future clinical investigations. ***Cancer* 1996; 77:635–9.**

KEYWORDS: hepatocellular carcinoma, antiandrogen, flutamide, hormonal therapy.

Hepatocellular carcinoma (HCC) is one of the most common cancers in Taiwan and in the world.[1,2] The overall prognosis of HCC is very poor. Surgical resection is the only potentially curative treatment for HCC and is most effective for small tumors.[3–5] Unfortunately, many HCC patients have tumor recurrence after surgery and most patients are not eligible for surgery because of advanced stage at presentation. Other treatments, such as conventional radiotherapy[6,7] or chemotherapy,[8–10] are ineffective and the results unsatisfactory. Embolization for HCC may be palliative.[11] Most of these treatments may have significant side effects. New, effective, and less toxic methods of treatment for patients with advanced HCC are urgently needed. HCC may be a hormone-dependent tumor and hormonal therapy has been recommended for further clinical investigations by several authors.[12–14]

HCC may be an androgen-dependent tumor. Patients with aplastic anemia who developed HCC after long term therapy with androgenic steroids were first reported by Johnson et al.[15] Thereafter, many androgen-induced HCCs were reported.[16–18] HCC was strongly associated with androgen in vitro and in vivo. Several rat hepatoma cell lines were reported to be androgen-dependent and contained cytoplastic androgen receptors (AR).[19] Androgen stimulates the growth of HCC cells implantated in rats when compared with controls.[20] AR were positive in 74% of male and 33% of female HCC patients.[21,22] Androgen may interact with AR of human HCC and enhance tumor growth and invasiveness. The recurrence rates

of HCC patients after hepatic resection were higher in AR positive patients[23] and the 5-year survival rate was significantly worse in AR positive HCC patients.[23] HCC is a male predominant disease and androgen may play a role in its development and prognosis. Survival in men was worse than in women after radical resection of HCC.[24] Two studies with small numbers of patients reported significant tumor regressions in a few HCC patients after they were treated with synthetic steroidal antiandrogens.[13,14] Therefore, the preliminary results of antiandrogen in the treatment of HCC is encouraging and warrants further clinical investigations.

Flutamide is a nonsteroidal antiandrogenic agent commonly used in the treatment of advanced prostate cancer. It has potent antiandrogenic effects by inhibiting androgen uptake and/or by inhibiting nuclear binding of androgen in target tissues. Flutamide is devoid of the adrenocortical, antiestrogen, progestational, or antifertility activity of steroidal antiandrogenic agents and does not have a marked inhibitory effect on libido and potency.[25,26] The purpose of this study was to investigate the clinical response and toxicity of flutamide in the treatment of patients with advanced HCC.

MATERIALS AND METHODS

Eligibility

Patients were required to have inoperable or metastatic HCC, which was measurable and pathologically confirmed. Patients who were not suitable for biopsy due to prolonged prothrombin time secondary to impaired liver function were required to have an alpha-fetoprotein level greater than 400 ng/mL and typical hepatic angiogram findings of HCC. Liver cirrhosis was verified by histology or by supporting biochemical data and compatible sonography or computerized tomography scan findings. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3. Patients who had previous surgery, embolization, or chemotherapy were eligible. The study protocol was reviewed and approved by the Hospital Ethics Committee. Each patient gave informed written consent.

Treatment Plan

Flutamide (Eulexin, 4′-nitro-3′-fluoromethylisobutyramilide, Schering Corporation, Kenilworth, NJ), 250 mg orally three times per day, was given. The treatment was continued for a minimum of 8 weeks or until evidence of progressive disease was found.

Evaluation

All patients had a thorough history and physical examination, complete blood counts, 12-channel sequential multiple analysis, prothrombin time, chest radiography, sonography, or computer tomography scan of the abdomen before therapy. HCC patients were staged according to the American Joint Committee on Cancer (AJCC) staging system.[27] Complete blood counts and sequential multiple analysis were repeated every 4 weeks. Chest radiography and sonography or computer tomography scan of the abdomen were conducted after 8 weeks of treatment. Responses and toxicities were assessed every 4 weeks according to the Eastern Cooperative Oncology Group criteria.[28] Complete response was defined as the disappearance of all measurable disease, without new lesions, for at least 4 weeks. Partial response was defined as a reduction of greater than 50% in the sum of the products of the greatest perpendicular diameters of measurable lesions and the absence of new lesions for at least 4 weeks. Stable disease was defined as a reduction of less than 50% or an increase of less than a 25% in tumor size without the appearance of new lesions for at least 4 weeks. Progressive disease was defined as an increase of greater than 25% in tumor size, or the occurrence of new lesions. All radiographic tumor measurements were reviewed independently by radiologists and gastroenterologists.

Statistical Methods

A two-stage Phase II design by Simon was used.[29] The study would be terminated if there were fewer than 2 responders in the first 22 patients tested in the first stage. Flutamide would be rejected as having a response rate of less than 10% with α of 0.05. The survival curve was plotted using the Kaplan–Meier method.[30]

RESULTS

Thirty-two patients with advanced HCC were studied. The patient characteristics are shown in Table 1. The median age was 66 years (range, 40 to 82 years). Thirty-one patients were male. All patients were cirrhotic. Cirrhosis was related to chronic hepatitis B and/or C virus infection in 28 patients, to alcohol in 1 patient, and was cryptogenic in 3 patients. All patients had AJCC Stage III or IV HCC. Twenty-nine patients had impaired liver functions as indicated by more than one of the following: a serum analine aminotransferase level of greater than twice the normal level, a serum bilirubin level of greater than 1.5 mg/dL, a serum albumin level of less than 3.0 gm/mL, and a prothrombin time greater than 1.25 international normalized ratio. Eighteen patients (56%) had main portal vein thrombosis and 9 patients (28%) had distant metastasis.

Ten patients died of HCC before repeat tumor measurements could be performed 8 weeks after flutamide therapy. Twenty-two patients were evaluable for response. The median duration of flutamide therapy was 8 weeks, (range, 1 to 26 weeks). There were no complete responses or partial responses. The 95% confidence inter-

TABLE 1
Patient Characteristics

Characteristic	No of patients
Total patients (male/female)	32 (31/1)
Median age (range)	66 (40-82)
Etiology of cirrhosis	
Hepatitis related	28
Alcohol	1
Cryptogenic	3
AJCC Stage III/IV	5/27
Performance status 0-2/3-4	31/1
ALT > 40 U/dL	26
Bilirubin > 1.5 mg/dL	16
Albumin < 3 g/dL	7
Prothrombin time > 1.25 INR	11
Main portal vein invasion	18
Extrahepatic metastasis	9
Previous treatment	
Surgery	2
Chemotherapy	5
Embolization	8

AJCC: American Joint Committee on Cancer; ALT: alanine aminotransferase.
INR: international normalized ratio.

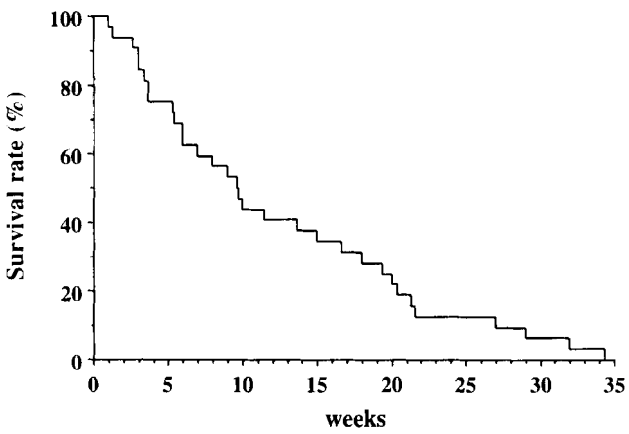

FIGURE 1. Overall survival curve of the 32 advanced hepatocellular carcinoma patients treated with flutamide.

val for the true response rate is 0, 15%.[31] Nine patients (41%) had stable disease. Thirteen patients (59%) had progressive disease. The alpha-fetoprotein level was reduced in 3 of 19 patients (10, 28, and 2149 ng/mL, respectively). The median survival of the 32 patients was 10 weeks (range, 1 to 35 weeks) (Fig. 1).

Overall toxicities of flutamide treatment in the 22 patients are shown in Table 2. All toxicities were mild and reversible. There were no major toxicities or treatment related deaths.

TABLE 2
Side Effects of Flutamide in 22 Evaluable Patients

	Grade of toxicity				
	0	1	2	3	4
Diarrhea	21	1 (4.5%)	0	0	0
Vomiting	20	2 (9.0%)	0	0	0
Gynecomastia	21	1 (4.5%)	0	0	0
Thromboembolism	22	0	0	0	0
Fever	22	0	0	0	0
Mucositis	22	0	0	0	0
Hair loss	22	0	0	0	0

DISCUSSION

There were in vitro and in vivo laboratory and clinical data to suggest that HCC may be an androgen-dependent tumor.[12-24] Hormonal therapy for HCC was recommended for further clinical investigations.[12-14] There are only two published studies of HCC patients treated with the antiandrogen cyproterone acetate, with encouraging results reported.[13,14] The first study by Forbes et al. reported a 20% (4 of 19 patients) objective response of HCC to cyproterone acetate treatment.[13] However, tumor volume was used for measurement of response instead of current standard criteria. If standard response criteria were used, the response rate may have been less than 20%. The median survival of 14 weeks suggests that cyproterone acetate treatment may have no clinical impact on survival. This is similar to the survival of patients with advanced HCC who receive no treatment or ineffective treatment.[4,8,13,32] The second study by Nagasue et al. reported a 19% (3 of 16 patients) objective response of HCC to cyproterone acetate treatment.[14] The definition of response was not stated in the report. Therefore, the true response rate was difficult to interpret. No survival data were provided. Furthermore, the numbers of patients in these two studies were very small. Therefore, no conclusions can be drawn from these studies. The true effectiveness of antiandrogen in the treatment of HCC patients remains uncertain.

This is the first report investigating a pure androgen receptor antagonist, flutamide, in the treatment of patients with advanced HCC using standard criteria to measure the anticancer response. The dose and schedule used in this study should be regarded as adequate and was exactly the same as that recommended for the effective antiandrogen treatment of prostatic cancer. In this study, flutamide appears to have no significant anticancer activity in the treatment of HCC patients. There was no complete response or partial response in 22 HCC patients after flutamide treatment. The rejection error must be less than 5% for flutamide to have a true anticancer effect

with a 15% response rate.[33] The median survival was 10 weeks in patients with advanced HCC after flutamide treatment. This is similar to the survival of patients with advanced HCC who receive no treatment or ineffective treatment.[4,8,13,32] All patients died within 35 weeks. The absence of long term survivors suggests that flutamide may not have major impact on the survival of patients with advanced HCC.

Despite data to suggest that HCC may be an androgen-dependent or androgen-responsive tumor, antiandrogen appears to have no significant clinical anticancer effects in the treatment of HCC patients in this study. We do not recommend it for current clinical use or future clinical investigations. Other new methods of treatment for HCC may warrant further investigations.

Side effects of flutamide therapy were minimal and well tolerated. Sporadic flutamide related hepatotoxicities had been reported in the treatment of prostate cancer patients.[34] The incidence of liver toxicity was very rare and occurred in only 4 of 1091 patients (0.36%).[35] In this study, no hepatotoxicity due to flutamide was observed.

In conclusion, HCC may not be an androgen-responsive tumor. Flutamide therapy has no significant anticancer activities in patients with advanced HCC.

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