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Randomized Controlled Trial of Tamoxifen in Advanced Hepatocellular Carcinoma

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ABSTRACT

Purpose
Randomized studies on tamoxifen treatment of hepatocellular carcinoma (HCC) produced conflicting results. The aim of this study was to assess the efficacy of tamoxifen administration in improving overall survival of patients with advanced HCC.

Patients and Methods
A total of 420 patients with HCC who were not suitable for surgery or local treatment were randomly assigned between April 1995 and May 2000: 210 in the control group and 210 in the tamoxifen group (20 mg/d orally). Patients with WHO performance status greater than 2, belonging to Child-Pugh class C, or with serum creatinine greater than 130 μmol/L were not eligible.

Results
Tolerance was good and the main reported adverse effects were thrombophlebitis (three patients), nausea (two patients), and hot flushes (three patients). Outcome did not differ between the two treatment arms: estimated median survival was 4.8 and 4.0 months in the tamoxifen and in the control groups, respectively (P = .25). Univariate analysis showed significant association of survival with age, Okuda stage, WHO performance status, Child-Pugh class, intrahepatic tumor stage, alpha-fetoprotein serum concentration, and presence of extrahepatic spread, portal vein thrombosis, hepatomegaly, or hepatalgia. In a Cox proportional hazards model we found a significant beneficial effect of tamoxifen on survival in patients belonging to Okuda I or II stages.

Conclusion
In this large study, tamoxifen did not improve the survival of patients with advanced HCC, but there is a suggestion that patients without major hepatic insufficiency seem to have some survival benefit. New trials involving this specific population are warranted.

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INTRODUCTION

Primary liver cancer is the fifth most common cancer and the third most common cause of cancer-related death in the world.[1] Hepatocellular carcinoma (HCC) is the most common form of liver cancer; incidence of HCC has substantially increased in developed countries during the last three decades[2,3]; this cancer is responsible for 6,000 deaths per year in France.[3] Despite the development of surveillance policy in cirrhotic patients, only a minority of patients with HCC can benefit from curative therapies.[4] For patients with advanced stages, the only therapeutic method that has shown a survival advantage is chemoembolization, but a clear benefit was only demonstrated in a subgroup of patients selected with restrictive criteria; in other patients with unresectable HCC, there is no standard therapy.[4]

Several lines of evidence have suggested an association between estrogen and liver cancer and an eventual role of tamoxifen in the treatment of inoperable HCC. Estrogen receptors are expressed in normal human liver, in chronic hepatitis, in benign hepatic tumor tissues, and (although rarely and at a low concentration) in HCC tumoral tissues.[5] Experimentally, estrogens are involved in stimulating hepatocyte proliferation in vitro and may act as liver tumor inducers or promoters in vivo.[6] The persistent administration of estrogens, particularly in the form of oral contraceptive, has been associated with an increased incidence of hepatic adenomas and with a small increased incidence of HCC.[5] The antiestrogenic compound tamoxifen has been shown to reduce the level of estrogen receptors in the liver, and to inhibit both hepatocyte proliferation after partial hepatectomy and HCC cell growth even through an estrogen-receptor–independent mechanism.[7] Variant estrogen receptors may be found in HCC, and are a strong prognostic factor for survival and determining response to antiestrogen therapy.[8]

From a clinical point of view, rare reports exist of regression of HCC during tamoxifen therapy,[9] but several comparative trials were conducted since 1990. When the present study was initiated in 1994, the results of three comparative trials were available showing a survival benefit in patients with advanced HCC treated with tamoxifen[10-12]; despite additional publication of large comparative studies that clearly were negative in terms of survival,[13-18] we decided not to close our study because of the following considerations: a limited number of patients were included in the initial studies; it was considered overall that the studies gave conflicting results, so that the use of tamoxifen therapy showed a large development in clinical practice; and above all, we considered the lack of evaluation of tamoxifen in patients with HCC that had developed in nonviral cirrhosis. The aim of our multicenter trial was to assess the efficacy of tamoxifen administration in improving overall survival in patients with advanced HCC who were not suitable for specific therapies.

PATIENTS AND METHODS

Patient Characteristics

The study conformed to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was reviewed and approved by the Ethics Review Committee of Picardie, Amiens, France. All patients provided written informed consent before enrollment onto the trial.

Eligibility criteria were HCC not suitable for surgical resection, liver transplantation, percutaneous ablation, or transarterial chemoembolization. Diagnosis of HCC was either cytologically or histologically confirmed, or made by the association of an established diagnosis of cirrhosis; demonstration in ultrasonography, and/or computed tomography scan, and/or MRI of a space-occupying lesion having an image consistent with the diagnosis of HCC; and persistently elevated alpha-fetoprotein (AFP) values above 500 μg/L. Exclusion criteria were age younger than 18 years, a serum creatinine greater than 130 μmol/L, a Child-Pugh class C, a WHO performance status greater than 2, and prior treatment with tamoxifen.

Between April 1995 and May 2000, 420 eligible patients from 78 French institutions were randomly assigned. Two hundred ten patients were assigned to the tamoxifen and the 210 patients were assigned to the control group. According to patient recruitment, we have defined a center variable: small centers included fewer than six patients and the other centers included six or more patients.

As shown in Tables 1 and 2, patients and tumor characteristics were well balanced between the two treatment groups. The mean age was 67.4 years (standard deviation [SD], 0.4 years). Most patients were men with underlying alcoholic cirrhosis. In both arms, cytologic or histologic tumor diagnosis was performed in a majority of patients. Previous treatments such as surgery, chemoembolization, percutaneous ethanol injection, or systemic chemotherapy were performed in 61 patients (14.5%).

Study Design and Random Assignment

Two French cooperative groups, Fédération Francophone de Cancérologie Digestive (FFCD) and Association Nationale des Gastroentérologues Hospitaliers, opened this multicenter phase III trial with two treatment arms. Between April 1995 and May 2000, eligible patients were registered at the FFCD center. They were randomly assigned between tamoxifen (study arm) and symptomatic treatment (control arm). Stratification was performed according to the institution guidelines, the type of prior treatment of HCC (none *v* surgery *v* chemoembolization *v* percutaneous ablation), the Okuda stage (stage I *v* II *v* III), and the WHO performance status (0/1 *v* 2).

Treatment

In the study group, tamoxifen was given orally at 20 mg per day (Kessar; Pharmacia S.A.S, Saint-Quentin en Yvelines, France) from the date of random assignment until death or inability to swallow the drug. Toxicity and patient's refusal were reasons for discontinuing or stopping treatment. All patients in the study group and in the control group received best supportive care and appropriate management of the liver disease as usually practiced in the individual centers; hormonal therapy, except tamoxifen in the study group, was the only forbidden medication.

Study Evaluations

The degree of liver function and the tumoral stage were evaluated according to the Child-Pugh classification[19] and the Okuda system, respectively.[20] Before random assignment, age, sex, diagnosis, and etiology of cirrhosis were assessed. Clinical examination and blood samples were obtained for blood cell counts; prothrombin time; serum creatinine; serum albumin; serum bilirubin; AST and ALT; alkaline phosphatase; gamma-glutamyl transpeptidase (GGT), hepatitis B surface antigen; anti–hepatitis B core, anti–hepatitis B surface, and anti–hepatitis C virus antibodies; and AFP determinations. Child-Pugh score and WHO performance status were staged. Thoracic fluoroscopy, upper GI tract endoscopic examination, and abdominal computed tomography scan were also obtained. Health-related quality of life was evaluated by the Spitzer quality-of-life index, which is a cancer-specific quality-of-life measurement. A score of 0 (worst) to 10 (best) was calculated after the patient

Table 1. Baseline Patient Characteristics

Characteristic	Tamoxifen (n = 210) No. of Patients	%	Control (n = 210) No. of Patients	%	P
Age, years					
Mean	67.5		67.3		.76
SD	0.6		0.6		
Male sex	186	88.6	189	90.0	.64
Underlying cirrhosis	190	90.5	182	86.7	.22
Etiology of cirrhosis					
Alcohol	139	73.2	142	78.0	.78
Hepatitis C virus	26	13.7	20	11.0	
Hepatitis B virus	11	5.8	11	6.0	
Other	8	4.2	5	2.8	
Unknown	6	3.2	4	2.2	
Child-Pugh class					
A	102	48.6	105	50.0	.25
B	86	41.0	93	44.3	
C	17	8.1	9	4.3	
Unknown	5	2.4	3	1.4	
WHO performance status					
0	46	21.9	31	14.8	.15
1	99	47.1	112	53.3	
2	65	31.0	67	31.9	
Ascites					
None	139	66.2	137	65.2	.36
Mild	57	27.1	54	25.7	
Moderate	14	6.7	19	9.1	
Encephalopathy					
Present	4	1.9	3	1.4	.99
Absent	206	98.1	207	98.6	
Hepatomegaly					
Present	154	73.3	168	80.0	.12
Absent	56	26.7	42	20.0	
Hepatalgia					
Present	43	20.5	66	31.4	.01
Absent	167	79.5	144	68.6	
Prothrombin time, %					
> 65	157	75.9	166	79.8	.57
40-65	48	23.1	41	19.7	
< 40	2	1.0	1	0.5	
Serum bilirubin, μmol/L					
< 35	160	77.7	158	76.3	.86
35-50	17	8.2	16	7.7	
> 50	29	14.1	33	15.9	
Serum albumin, g/L					
< 28	48	23.7	24	11.5	.004
28-35	77	37.9	100	48.1	
> 35	78	38.4	84	40.4	

Abbreviation: SD, standard deviation.

Table 2. Baseline Tumor Characteristics

Characteristic	Tamoxifen (n = 210) No. of Patients	%	Control (n = 210) No. of Patients	%	P
Type of diagnosis					
Cytologic or histologic	122	58.1	130	61.9	.43
Imaging + AFP > 500 μg/L	88	41.9	80	38.1	
Okuda stage					
I	71	33.8	74	35.2	.86
II	119	56.7	119	56.7	
III	20	9.5	17	8.1	
AFP categories, μg/L					
≤ 5	42	20.5	59	28.9	.12
6-250	59	28.8	63	30.9	
251-5,000	63	30.7	53	26.0	
> 5,000	41	20.0	29	14.2	
Portal vein thrombosis					
Absent	122	58.7	129	62.6	.41
Present	86	41.3	77	37.4	
Involved liver volume, %					
≤ 50	148	70.5	141	67.1	.76
> 50	62	29.5	69	32.9	
Metastatic spread					
Absent	174	82.9	174	82.9	.99
Present	36	17.1	36	17.1	
Previous treatment					
None	181	86.2	179	85.2	.78
Surgery	8	3.8	8	3.8	.88
Chemoembolization	14	6.7	14	6.7	.81
Percutaneous ethanol injection	7	3.3	8	3.8	.88
Systemic chemotherapy	0	0.0	2	0.9	.16

Abbreviation: AFP, alpha fetoprotein.

answered the five items of the questionnaire in the areas of activity, daily life, health perceptions, social support, and behavior. Each area was assessed with one item, rated on a 3-point scale.[21]

Patient follow-up was planned every 3 months until death or treatment was stopped; at each follow-up, clinical examination and blood samples were obtained for blood cell count, prothrombin time, serum creatinine, serum albumin, serum bilirubin, ALT and AST, alkaline phosphatase, and GGT; Child-Pugh score, WHO performance status, and Spitzer quality-of-life index were also assessed.

Information on toxicity and adverse events was systematically collected during treatments. We report those potentially due to tamoxifen treatment and not those probably due to tumoral progression or underlying cirrhosis.

Statistical Analysis

The primary end point was overall survival (OS). The planned sample size of 420 patients was calculated with a two-tailed type I error of 5% and a statistical power of 80%, and the following hypotheses: an expected median survival of 6 months in the control group and 8 months in the tamoxifen-treated group. The patients were recruited during 36 months and a minimal duration of 12 months of follow-up was planned. OS was defined as the interval between the date of random assignment to treatment and the date of death or the last follow-up information for living patients. Data were analyzed on in intent-to-treat principle.

At inclusion, the clinical variables were described as mean (± SD) or frequencies, and respectively compared with the Student's *t* test or the Pearson χ^2.

Survival curves were estimated by the Kaplan-Meier method and compared by the log-rank test. Relative hazard of death and

95% CI adjusted by the main prognostic factors were estimated by Cox's proportional hazards model. An exploratory subgroup analysis was also performed among patients with Okuda I or II stages. The Spitzer quality-of-life index was described and compared at baseline and during 9 months (three follow-up assessments) in each arm. A mean difference among available scores was calculated and compared between baseline and each of these follow-up assessments.

RESULTS

Treatment

Among the 210 patients assigned to receive tamoxifen, 14 (6.6%) have stopped taking the drug. The other 96 patients continued until death or until they were unable to swallow. The reasons for discontinuing tamoxifen were toxicity (n = 6), refusal (n = 4), and severe intercurrent extrahepatic disease (n = 4). Of 210 patients enrolled onto the control group, five (2.4%) took tamoxifen.

Toxicity

Eleven (5.2%) patients have developed a tamoxifen-related toxicity. Reported adverse effects were thrombophlebitis (three patients); hot flushes (three patients); nausea (two patients); and dizziness, headache, and sexual impotence (one patient each).

Survival

By November 15, 2000, 392 patients (93.3%) had died. The main causes of death (listed in Table 3) were tumor progression and hepatorenal syndrome. According to treatment arm, there were no differences in overall survival (Fig 1): estimated median survival was 4.8 months (SD, 0.6 months) and 4.0 months (SD, 0.5 months) in the tamoxifen and in the control groups, respectively ($P = .25$), and the 1-year survival probability was 22.8% (SD, 3.0%) and 19.9% (SD, 2.8%), respectively. Univariate analysis showed significant association of survival with age, Okuda stage, WHO performance status, Child-Pugh class, intrahepatic tumor stage, presence of extrahepatic spread of the tumor, presence of portal vein thrombosis, AFP serum concentration, and presence of hepatomegaly or hepatalgia (Table 4).

Table 3. Causes of Death (some patients had several causes of death)

Cause of Death	Tamoxifen No. of Patients	Tamoxifen %	Control No. of Patients	Control %	*P*
Total deaths	194		198		
Deaths of known origin	175		172		
Tumor progression	110	62.9	114	66.3	.86
Hepatorenal syndrome	64	36.6	64	37.2	.89
GI bleeding	28	16.0	29	16.9	.95
Metastasis	20	11.4	24	14.0	.57
Other	37	21.1	34	19.8	.63

After adjustment for prognostic factors, in comparison with the control group, patients receiving tamoxifen had a lesser probability of death. However, this relative hazard ratio of death among overall patients was not significant (hazard ratio, 0.83; 95% CI, 0.68 to 1.02; $P = .074$; Table 5). The clinical factors that independently influenced OS were Okuda stage, AFP serum concentration, WHO performance status, portal vein thrombosis, and hepatomegaly (Table 5). In comparison with the Okuda I patients, the Okuda II and Okuda III patients have a significantly greater risk of death: relative risk (RR), 1.51 (95% CI, 1.20 to 1.90) and RR, 3.03 (95% CI, 2.07 to 4.43), respectively. AFP serum concentration greater than 5 μg/L was significantly associated with a poor survival probability: the RR of death was 1.75 (95% CI, 1.32 to 2.32) for patients with AFP more than 5 and $\leq$ 250 μg/L, and 1.89 (95% CI, 1.45 to 2.47) for patients with AFP more than 250 μg/L. The presence of a portal vein thrombosis and hepatomegaly had a negative impact on OS: RR, 1.44 (95% CI, 1.16 to 1.79) and RR, 1.37 (95% CI, 1.07 to 1.77), respectively.

The results of exploratory analysis in patients belonging to Okuda I or II stages using a multivariate Cox proportional hazards model highlighted a significant beneficial effect of tamoxifen on OS: RR, 0.79 (95% CI, 0.4 to 0.98; $P = .033$; Table 5). Despite this result, the same clinical factors in the overall patient analysis influenced survival probability: Okuda stage, AFP serum concentration, WHO performance status, portal vein thrombosis, and hepatomegaly (Table 5).

Quality of Life

Data describing the Spitzer quality-of-life index at baseline and during follow-up are shown in Table 6. According to baseline, among patients with follow-up, the mean Spitzer index globally decreased during 9 months. In the tamoxifen and control group, the decrease in scores represented 11% (−1.14 points) and 9% (−0.93) of the theoretical range score, respectively.

DISCUSSION

In our study, HCC patients treated with tamoxifen had the same OS as patients who never took this drug. The quality of life seemed to be similar. These negative results are consistent with the state of the art from literature regarding hormonal therapy of HCC.[4] In the 1990s, three controlled studies showed significantly improved survival in patients treated with tamoxifen.[10-12] Therefore, this drug has been widely used in clinical practice, especially because of its low cost, low incidence of adverse effects, and the lack of a potential useful therapeutic approach in patients with inoperable HCC. Then, two meta-analysis studies of the few available clinical trials reporting a significant 1-year survival

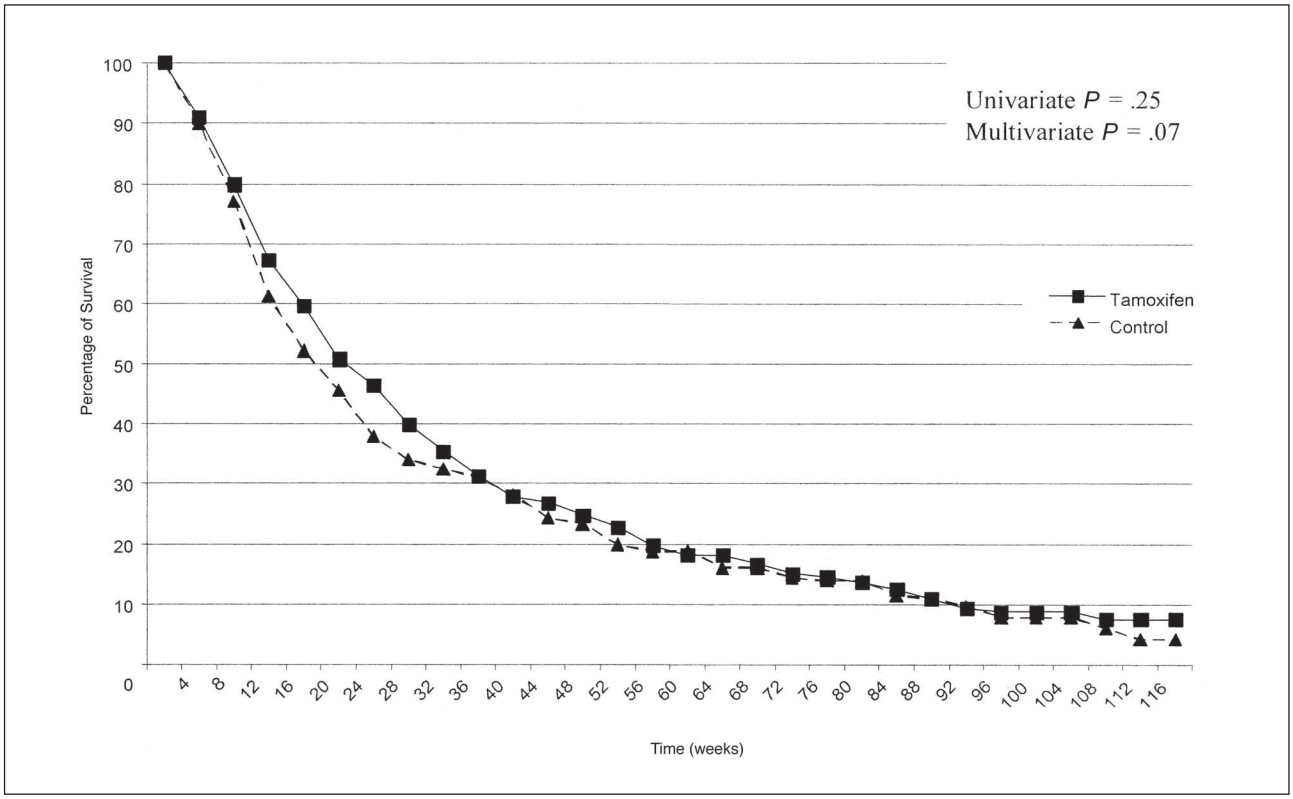

Fig 1. Kaplan and Meier estimated probability of survival in patients administrated tamoxifen (n = 210) and in controls (n = 210).

advantage with tamoxifen seemed to confirm the initial reports.[22,23] It must be emphasized that the positive studies suffered from important statistical bias: two were nonblinded studies,[10,11] one was not a randomized study,[10] and above all, they included a small number of patients (38, 36, and 22 patients, respectively), causing a high type I risk.

In 1995, a somewhat confusing result was obtained from a study reporting a significant improvement of 1-year survival rate without improvement of the median survival time in patients treated with tamoxifen.[14] From 1995 to 2002, five large negative randomized studies (four of which were double-blind trials) from a total of 1,144 patients were clearly negative in terms of survival and contradicted the promising results reported in the 1990s.[13-18] Finally, the updating of one previous meta-analysis,[15] the 5-year results of a previously negative randomized trial,[24] and the recent publication of a negative meta-analysis including all randomized studies confirm that tamoxifen imparts no antitumoral effect and no survival benefit in patients with HCC.[25]

The publication in the recent 10 years of conflicting and confusing results from a clinical point of view, and the great number of studies needed before a final conclusion can be drawn, must serve as a strong incitement for the readers to focus high-quality trials and for the researchers to plan clinical trials. This conclusion is in accordance with the recommendations of the Barcelona-2000 European Association for the Study of the Liver conference regarding the necessity to assess efficacy of treatment of HCC in multicenter, large, randomized controlled trials.[26]

In comparison with other large, randomized, negative studies, our trial included somewhat different patients: in the Cancer of the Liver Italian Program (CLIP) study, the patients were not exclusively in palliative condition, as were our patients (47% of the 237 patients in the CLIP study were administered tamoxifen associated with a locoregional treatment, and median survival in the control group was 16 months).[15] Our study was conducted in the French population in which HCC is mainly developed in alcoholic cirrhosis, whereas previous studies essentially focused on HCC developed in postviral cirrhosis.[11,13-15,17,18] The multivariate analyses highlighted the same prognostic factors as the other studies, suggesting robustness of our data and our results. Okuda stage, AFP serum concentration, WHO performance status, portal vein thrombosis, and hepatomegaly were the main clinical factors influencing OS.

Our study may have some limitations. First, it was not a double-blind trial versus placebo, but this deficiency is probably of marginal importance in a study for which the sole criterion was global survival. Second, there was no evaluation of objective response according to radiologic or biochemical criteria; in a phase II study and in many phase III studies, including the positive studies, it was reported

Table 4. Overall Survival According to Patients' Baseline Characteristics in Univariate Analysis

Baseline Parameters	Median Survival (months)	SD	*P*
Sex			
Male	4.2	0.3	.43
Female	6.5	1.6	
Center			
Small, < 6 patients	4.1	0.2	.047
Others, ≥ 6 patients	5.6	0.4	
Age, years			
< 70	3.4	0.4	.0012
≥ 70	5.9	0.7	
Okuda stage			
I	7.6	1.8	.0001
II	3.9	0.4	
III	1.4	0.2	
WHO performance status			
0	8.5	0.9	.0001
1	4.3	0.3	
2	2.4	0.3	
Child-Pugh class			
A	5.9	0.6	.0001
B	3.1	0.4	
C	1.5	0.8	
Metastatic spread			
Absent	4.4	0.4	.007
Present	3.3	0.9	
AFP, μg/L			
≤ 5	8.2	1.3	.0001
≤ 250	4.1	0.5	
> 250	3.5	0.5	
Treatment			
Tamoxifen	4.8	0.6	.25
Control	4.0	0.5	
Hepatomegaly			
Present	2.9	1.0	.0002
Absent	8.5	0.3	
Hepatalgia			
Present	2.5	0.4	.0005
Absent	5.1	0.3	
Prior treatment			
None	4.2	0.3	.32
Yes	5.7	0.7	
Involved liver volume, %			
≤ 50	5.0	0.5	.0001
> 50	3.4	0.6	
Portal vein thrombosis			
Absent	5.9	0.5	.0001
Present	2.9	0.3	

Abbreviations: SD, standard deviation; AFP, alpha fetoprotein.

that this event is extremely rare.[10,11,13,14,17] Third, we choose not to perform the assessment of estrogen receptors in the tumors because we considered that the cost of the procedure and the need for liver biopsy might reduce the inclusion rate in the trial.

At the beginning our trial, it seemed that the priority was to conduct promptly an easy to perform trial, in terms of feasibility and cost, to solve the conflicting results of published data. According to eligibility criteria, 23 patients (10.5%) in the tamoxifen group and 12 patients (5.7%) in the control group, respectively, belonged to the Child-Pugh class C or had an undetermined Child-Pugh score at the date of inclusion. However, these patients were considered initially by the investigators to have fulfilled the inclusion criteria. We have ultimately decided to include these patients in our analysis because they represented only a minority of patients and were well balanced in the two arms of the study. Although randomization globally allowed a well-balanced repartition of patients and tumor characteristics between the two groups, it is noteworthy that serum albumin was significantly lower in the treatment group. However, it is unlikely that this difference counteracted the results of the trial. On one hand, other parameters assessing hepatic function, and particularly the most valid means of assessing prognosis in patients with cirrhosis—the Child-Pugh classification—were equally divided among the two groups. On the other hand, all parameters assessing tumor development were well balanced. Finally, the dosage of 20 mg per day of tamoxifen may be considered low, but it is known that even a small dose of tamoxifen is able to block all of the estrogen receptors, and because this drug has a long biologic half-life, it accumulates during long-term administration, making the low doses relevant.[27] Conversely the tamoxifen dosage was higher in three large negative studies,[15-17] and speculating on a therapeutic effect of tamoxifen independent of estrogen receptors, a recent trial evaluating the effect of high-dose tamoxifen found that it does not prolong survival and even may have a negative impact.[18]

It has been proposed that the growth of HCC is modulated by estrogens, offering the rationale for evaluating the efficacy of estrogen receptor blockage by tamoxifen. Lack of tamoxifen efficacy in terms of tumor growth and survival could be ascribed either to a low expression of estrogen receptors in HCC[28] or to the expression of mutated estrogen receptors, which is known to be associated with male sex, unfavorable prognosis, high tumoral growth, and inefficacy of tamoxifen.[8] However, a study recently suggested that the effect of tamoxifen treatment is not affected by the expression of hormone receptors.[17]

Despite these main results, we have observed a better survival in a subgroup of patients with relatively preserved condition as assessed by Okuda stage I or II. Because this is a result of subgroup analysis, this finding must be regarded with great caution. On one hand, a favorable influence of liver disease severity on the efficacy of tamoxifen treatment was not observed in previous studies.[10,13-16] On the other hand, this effect was demonstrated in an a posteriori defined group; the data cannot be considered as evidence in favor of treatment and only provides a rationale for testing tamoxifen in this subgroup of patients in a randomized controlled study. This positive result among Okuda I and

Table 5. Multivariate Cox Proportional Hazards Risk Analysis

Parameter	Model 1, Okuda I/II/III (n = 420)			Model 2, Okuda I/II (n = 383)		
	RR	95% CI	*P*	RR	95% CI	*P*
Treatment						
Control group	1			1		
Tamoxifen	0.83	0.68 to 1.02	.074	0.79	0.64 to 0.98	.033
Center						
Others, ≥ 6 patients	1			1		
Small, < 6 patients	1.10	0.90 to 1.35	.36	1.14	0.92 to 1.41	.24
Sex						
Female	1			1		
Male	1.39	1.00 to 1.94	.042	1.33	0.94 to 1.89	.09
WHO performance status						
0	1			1		
1	1.40	1.05 to 1.86	.02	1.37	1.02 to 1.83	.030
2	1.96	1.44 to 2.68	.0001	1.81	1.32 to 2.49	.0002
Okuda stage						
I	1			1		
II	1.51	1.20 to 1.90	.0004	1.55	1.23 to 1.95	.0002
III	3.03	2.07 to 4.43	.0001			
Hepatomegaly						
No	1			1		
Yes	1.37	1.07 to 1.77	.012	1.32	1.01 to 1.71	.035
AFP, μg/L						
≤ 5	1			1		
≤ 250	1.75	1.32 to 2.34	.0001	1.83	1.36 to 2.47	.0001
> 250	1.89	1.45 to 2.47	.0001	1.98	1.50 to 2.62	.0001
Portal vein thrombosis						
No	1			1		
Yes	1.44	1.16 to 1.79	.0011	1.66	1.33 to 2.07	.0001

Abbreviations: RR, relative risk; AFP, alpha fetoprotein.

II patients could be explained by the fact that Okuda III patients have a low probability to obtain a survival benefit. The potential antitumoral effect of tamoxifen could be counterbalanced by the negative impact of the disease evolution. For example, major vascular tumor invasion with or without hepatic failure could reduce the beneficial effect of tamoxifen. Another explanation could be that the clinical variability was more controlled without Okuda III patients. Another possible explanation is that statistical power was optimized. For example, we observed a larger number of patients who have elevated AFP greater than 250 μg/L in the treatment than in control arm. In this regard, we discussed

Table 6. Description of the Spitzer Quality-of-Life Index During Follow-Up According to Treatment Arms

Follow-up	Tamoxifen Spitzer QoL Index			Control Spitzer QoL Index			
	No. of Patients	Mean	SD	No. of Patients	Mean	SD	*P*
Baseline	180	7.97	1.69	148	8.04	1.48	.72
3rd month	147	6.54	2.64	117	6.82	2.48	.57
6th month	76	6.59	2.65	70	7.01	2.45	.32
9th month	43	7.14	2.5	45	7.11	2.49	.46
Mean difference between baseline							
3rd month	147	−1.43	2.54	117	−1.22	2.17	.49
6th month	76	−1.68	2.83	70	−1.12	2.39	.20
9th month	43	−1.14	2.45	45	−0.93	2.31	.69

Abbreviations: QoL, quality of life; SD, standard deviation.

pragmatically the interest of including Okuda III patients in our study and future studies.

In conclusion, this study confirmed that tamoxifen is not effective in prolonging survival of patients with advanced HCC in those with cirrhosis of various etiologies. The result of an experimental study supports a clinical trial of tamoxifen as a chemopreventive agent in humans with chronic liver disease.[29] From a practical point of view, HCC remains a significant clinical challenge; many patients are still diagnosed at a nonsurgical stage so that curative methods such as hepatic liver transplantation, hepatic resection, and percutaneous ablation can be proposed only to a minority of patients. For those patients diagnosed at an advanced stage, arterial chemoembolization has been demonstrated to prolong survival, but this method can be performed only among to a small proportion of asymptomatic patients with a preserved liver function. For other patients with advanced HCC there is no standard therapy, given that chemotherapy, interferon therapy, and antiandrogen therapy are ineffective.[4] Regarding tamoxifen, large clinical trials using somatostatin analogs do not seem to confirm initial promising results of small randomized trials.[30,31] There is an obvious and urgent need for clinical trials evaluating new treatment options such as the novel targeted agents BAY 43-9006,[32] gefitinib,[33] and pravastatin.[34]

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al: Estimating the world cancer burden: GLOBOCAN 2000. Int J Cancer 94:153-156, 2001
2. El-Serag HB, Davila JA, Petersen NJ, et al: The continuing increase in the incidence of hepatocellular carcinoma in the United States: An update. Ann Intern Med 139:817-823, 2003
3. Remontet L, Estève J, Bouvier A-M, et al: Cancer incidence and mortality in France over the period 1978-2000. Rev Epidemiol Sant é Publique 51:3-30, 2003
4. Llovet JM, Burroughs A, Bruix J: Hepatocellular carcinoma. Lancet 362:1907-1917, 2003
5. Clavière C, Bronowicki JP, Hudziak H, et al: Roles of sex steroids and their receptors in the pathophysiology of hepatocellular carcinoma. Gastroenterol Clin Biol 22:73-86, 1998
6. Francavilla A, Polimeno L, DiLeo A, et al: The effect of estrogen and tamoxifen on hepatocyte proliferation in vivo and in vitro. Hepatology 9:614-620, 1989
7. Jiang SY, Shyu RY, Yeh MY, et al: Tamoxifen inhibits hepatoma cell growth through an estrogen receptor independent mechanism. J Hepatol 23:712-719, 1995
8. Villa E, Moles A, Ferretti I, et al: Natural history of inoperable hepatocellular carcinoma: Estrogen receptors' status in the tumor is the strongest prognostic factor for survival. Hepatology 32:233-238, 2000
9. Macaigne G, Auriault ML, Boivin JF, et al: Regression of hepatocellular carcinoma under tamoxifen: Report of one case and review of the literature. Gastroenterol Clin Biol 26:1165-1167, 2002
10. Farinati F, Salvagnini M, de Maria N, et al: Unresectable hepatocellular carcinoma: A prospective controlled trial with tamoxifen. J Hepatol 11:297-301, 1990
11. Martinez Cerezo FJ, Tomàs A, Donoso L, et al: Controlled trial of tamoxifen in patients with advanced hepatocellular carcinoma. J Hepatol 20:702-706, 1994
12. Elba S, Giannuzzi V, Misciagna G, et al: Randomized controlled trial of tamoxifen versus placebo in inoperable hepatocellular carcinoma. Ital J Gastroenterol 26:66-68, 1994
13. Castells A, Bruix J, Bru C, et al: Treatment of hepatocellular carcinoma with tamoxifen: A double-blind placebo controlled trial in 120 patients. Gastroenterology 109:917-922, 1995
14. Manesis EK, Giannoulis G, Zoumboulis P, et al: Treatment of hepatocellular carcinoma with combined suppression and inhibition of sex hormones: A randomized controlled trial. Hepatology 21:1535-1542, 1995
15. CLIP Group: Tamoxifen in treatment of hepatocellular carcinoma: A randomised controlled trial. Lancet 352:17-20, 1998
16. Riestra S, Rodriguez M, Delgado M, et al: Tamoxifen does not improve survival of patients with advanced hepatocellular carcinoma. J Clin Gastroenterol 26:200-203, 1998
17. Liu CL, Fan ST, Oi-Lin Ng I, et al: Treatment of advanced hepatocellular carcinoma with tamoxifen and the correlation with expression of hormones receptors: A prospective randomized study. Am J Gastroenterol 95:218-222, 2000
18. Chow PKH, Tai BC, Tan CK, et al: High-dose tamoxifen in the treatment of inoperable hepatocellular carcinoma: A multicenter randomized controlled trial. Hepatology 36:1221-1226, 2002
19. Pugh RNH, Murray-Lyon IM, Dawson JL, et al: Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 60:646-649, 1973
20. Okuda K, Ohtsuki T, Obata H, et al: Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Cancer 56:918-926, 1985
21. Spitzer WO, Dobson AJ, Hall J, et al: Measuring the quality of life of cancer patients: A concise QL-index for use by physician. J Chronic Dis 34:585-597, 1981
22. Simonetti RG, Liberati A, Angiolini C, et al: Treatment of hepatocellular carcinoma: A systematic review of randomized controlled trials. Ann Oncol 8:117-136, 1997
23. Mathurin P, Rixe O, Carbonell N, et al: Review article: Overview of medical treatments in unresectable hepatocellular carcinoma-an impossible meta-analysis? Aliment Pharmacol Ther 12:111-126, 1998
24. Perrone F, Gallo C, Daniele B, et al: Tamoxifen in the treatment of hepatocellular carcinoma: 5-years results of the CLIP-1 multicentre randomised controlled trial. Curr Pharm Des 8:1013-1019, 2002
25. Llovet JM, Bruix J, for the Barcelona-Clinic-Liver Cancer Group: Systematic review of randomized controlled trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 37:429-442, 2003
26. Bruix J, Sherman M, Llovet JM, et al: Clinical management of hepatocellular carcinoma: Conclusions of the Barcelona-2000 EASL Conference. J Hepatol 35:421-430, 2001
27. Jordan VC: Antiestrogens in cancer treatment, in Stoll BA (ed): Endocrine Management of Cancer. Basel, Switzerland, Karger, 1988, pp 57-64
28. Nagasue N, Yu L, Yukala H, et al: Androgen and oestrogen receptors in hepatocellular

carcinoma and surrounding liver parenchyma: Impact on intrahepatic recurrence after hepatic resection. Br J Surg 82:542-547, 1995

29. Di Bisceglie AM, Osmack P, Brunt EM: Chemoprevention of hepatocellular carcinoma by tamoxifen. Hepatology 36:697A, 2002 (abstr 2136)

30. Kouroumalis E, Skordilis P, Thermos K, et al: Treatment of hepatocellular carcinoma with Octreotide: A randomised controlled study. Gut 42:442-447, 1998

31. Yuen MF, Poon RT, Lai CL, et al: A randomized placebo-controlled study of long-acting octreotide for the treatment of advanced hepatocellular carcinoma. Hepatology 36:687-691, 2002

32. Strumberg D, Richly H, Hilger RA: Phase I clinical and pharmacokinetic study of the novel raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43-9006 in patients with advanced refractory solid tumors. J Clin Oncol 23:965-972, 2005

33. Schiffer E, Housset C, Cacheux W, et al: Gefitinib, an EGFR inhibitor, prevents hepatocellular carcinoma development in the rat liver with cirrhosis. Hepatology 41:307-314, 2005

34. Kawata S, Yamasaki E, Nagase T, et al: Effects of pravastatin on survival in patients with advanced hepatocellular carcinoma: A randomized controlled trial. Br J Cancer 84:886-891, 2001