Tamoxifen in treatment of hepatocellular carcinoma: a randomised controlled trial

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Summary

Background Results from small randomised trials on tamoxifen in the treatment of hepatocellular carcinoma (HCC) are conflicting. We studied whether the addition of tamoxifen to best supportive care prolongs survival of patients with HCC.

Methods Patients with any stage of HCC were eligible, irrespective of locoregional treatment. Randomisation was centralised, with a minimisation procedure accounting for centre, evidence of disease, and time from diagnosis. Patients were randomly allocated best supportive care alone or in addition to tamoxifen. Tamoxifen was given orally, 40 mg per day, from randomisation until death.

Results 496 patients from 30 institutions were randomly allocated treatment from January, 1995, to January, 1997. Information was available for 477 patients. By Sept 15, 1997, 119 (50%) of 240 and 130 (55%) of 237 patients had died in the control and tamoxifen arms, respectively. Median survival was 16 months and 15 months (p=0·54), respectively. No differences were found within subgroups defined by prognostic variables. Relative hazard of death for patients receiving tamoxifen was 1·07 (95% CI 0·83–1·39).

Interpretation Our findings show that tamoxifen is not effective in prolonging survival of patients with HCC.

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Introduction

The results of systemic treatments of hepatocellular carcinoma (HCC) have been disappointing. There is no standard systemic therapy and few treatments have been adequately tested in randomised trials.

Animal models of liver carcinogenesis and epidemiological studies in human beings[1] have suggested close associations between sex hormones and primary liver cancer. Oestrogens may have a role as inducer and promoter in liver carcinogenesis.[2,3] The antioestrogenic compound tamoxifen counteracts some of the effects of oestrogen[4] and inhibits hepatocyte proliferation.[5]

When we planned this study, the results of three comparative trials on the efficacy of tamoxifen in the treatment of HCC had been published.[6–8] All of these trials were limited to patients with advanced HCC and very poor residual liver function, and yielded positive results. A further randomised trial by Castells and colleagues,[9] still small and limited to patients with advanced disease, did not find any significant survival advantage with tamoxifen. A systematic review of the above randomised studies,[10] accounting for data retrieved from a total of 216 patients who had taken part in randomised tamoxifen trials, still yielded a positive result with a pooled odds ratio of surviving at 1-year of 2·0 (95% CI 1·1–3·6) for patients on tamoxifen. However, because all the published trials had several methodological drawbacks, the authors of the meta-analysis suggested a note of caution in considering these results conclusive and called for a large randomised trial.

Our aim was to evaluate whether treatment with tamoxifen could improve survival of patients with HCC. A pragmatic approach was chosen: eligibility criteria were broad, overall survival was the only endpoint of the intention-to-treat analysis, no placebo was planned in the control arm and no additional follow-up rule was added to the usual clinical practice of participating institutions.

Methods

All patients with HCC who had a life expectancy longer than 3 months, as subjectively assessed by the investigator, were eligible for the study. Diagnosis of HCC had to be either cytologically or histologically confirmed, or a positive sonography or computed-tomography scan with alpha-fetoprotein (AFP) serum concentrations greater than 400 ng/mL was needed. Exclusion criteria were diagnosis made more than 2 years before randomisation, previous treatment with tamoxifen, and lack of informed consent. The protocol was approved by ethics committees of participating institutions.

In the study group, tamoxifen was given orally at 40 mg per day from the date of randomisation until death or inability of the patient to swallow it. Toxicity and patient's refusal were also reasons for discontinuing treatment. In both the study group and the control group, investigators were free to choose supportive care and local treatment.

The planned sample size was about 480 patients. This number was calculated on the basis of: expected 1-year survival in the control group being 50%; minimum detectable difference

	Tamoxifen (n=237)	Control (n=240)	Total (n=477)
Median (range) age (years)	66 (38–91)	67 (31–85)	67 (31–91)
Men	169 (71·3%)	183 (76·2%)	352 (73·8%)
Evidence of disease at entry	218 (92·0%)	223 (92·5%)	441 (92·5%)
Interval between diagnosis and entry			
0–6 months	194 (81·9%)	199 (82·9%)	393 (82·4%)
7–12 months	21 (8·9%)	19 (7·9%)	40 (8·4%)
13–24 months	22 (9·3%)	22 (9·2%)	44 (9·2%)
Underlying chronic liver disease			
Cirrhosis	219 (92·4%)	219 (91·2%)	438 (91·8%)
Chronic hepatitis	12 (5·1%)	16 (6·7%)	28 (5·9%)
None	6 (2·5%)	5 (2·1%)	11 (2·3%)
Cause of liver disease			
Viral	212 (89·4%)	210 (87·5%)	422 (88·5%)
B virus	23 (10·9%)	24 (11·4%)	47 (11·2%)
C virus	180 (84·9%)	164 (78·1%)	344 (81·5%)
B+C virus	9 (4·2%)	22 (10·5%)	31 (7·3%)
Alcoholic	7 (3·0%)	6 (2·5%)	13 (2·7%)
Other	0	2 (0·8%)	2 (0·4%)
Unknown	18 (7·6%)	22 (9·2%)	40 (8·4%)
Child-Pugh category			
A	101 (42·6%)	105 (43·8%)	206 (43·2%)
B	95 (40·1%)	86 (35·8%)	181 (37·9%)
C	25 (10·5%)	35 (14·6%)	60 (12·6%)
Unknown	16 (6·8%)	14 (5·8%)	30 (6·3%)
Mean (SD) serum bilirubin (mg/dL)	2·5 (4·7)	1·9 (1·9)	2·2 (3·6)
Mean (SD) serum albumin (g/dL)	3·5 (0·6)	3·5 (0·5)	3·5 (0·6)
Mean (SD) prothrombin activity	74% (17)	73% (17)	73% (17)

Table 1: **Characteristics of patients**

in the tamoxifen arm being 11% above or below that of the contol group; planned duration of enrolment being 2 years; planned duration of follow-up after closing the enrolment being 8 months; planned rates of loss of patient being 5%; statistical power being 80%; and two-tailed type I error of 5%. SOLO Statistical System Power Analysis software (BMDP Statistical Software, Cork, Ireland, 1991) was used for sample-size calculation.

Randomisation was centralised at the data coordinating centre. The investigators telephoned the patients who were then assigned treatments according to a minimisation procedure[11] with centre, evidence of disease at entry (yes/no), and time from diagnosis (<7 months, 7–12 months, or >12 months) as stratification variables.

The only endpoint for the analysis was overall survival, defined as the interval between the date of randomisation and the date of death or last follow-up information for living patients. Data were analysed on an intention-to-treat basis. All patients for whom follow-up information was available were included in the analysis, irrespective of their eligibility.

Survival curves were drawn by the Kaplan-Meier method and compared by the Mantel-Haenszel test. Relative hazard of death and 95% CI adjusted by known prognostic factors (local treatment, Child-Pugh's and Okuda's categories) were estimated by Cox's proportional hazards model. Interactions between treatment and covariates were also tested in the multivariate analysis to check for possible differences of effect within prognostic subgroups. No interim analyses were planned.

The previous meta-analysis of tamoxifen versus no active treatment[10] was updated with the same Peto method.[12]

Results

Table 1 shows the patients' characteristics. Overall, 496 patients were randomly allocated treatment between January, 1995, and January, 1997, from 30 Italian institutions (figure 1). 19 (3·8%) patients, 11 in the tamoxifen arm and eight in the control arm, were excluded because no information was given to the coordinating centre. There were 477 patients who could be evaluated. 22 patients were found ineligible after
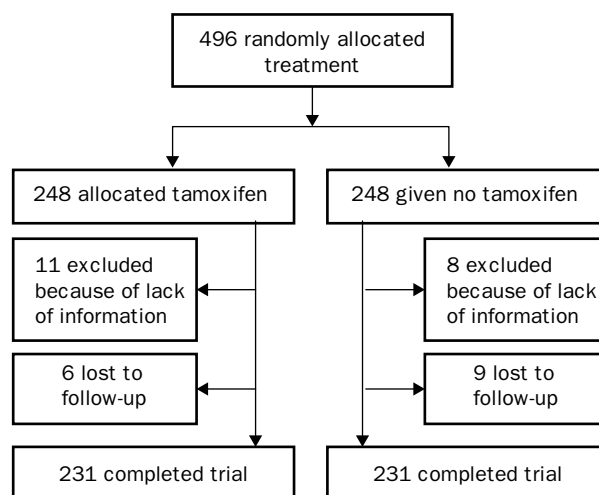

Figure 1: **Trial profile**

randomisation: 18 because of lack of cytological or histological confirmation with AFP serum concentrations lower than 400 ng/mL; two because there had been more than 2 years since diagnosis; and two because of previous treatment with tamoxifen. These patients were included in the analyses.

Of the 477 patients, 237 were assigned to the tamoxifen group and 240 to the control group (figure 1). All patients (table 1) and characteristics of the tumours (table 2) were well balanced between the two treatment groups. Most patients were men with underlying viral

	Tamoxifen (n=237)	Control (n=240)	Total (n=477)
Type of diagnosis			
Cytological or histological	191 (80·6%)	203 (84·6%)	394 (82·6%)
Imaging+AFP>400	36 (15·2%)	29 (12·1%)	65 (13·6%)
Imaging only	10 (4·2%)	8 (3·3%)	18 (3·8%)
Okuda stage			
I	107 (45·1%)	101 (42·1%)	208 (43·6%)
II	79 (33·3%)	90 (37·5%)	169 (35·4%)
III	21 (8·9%)	14 (5·8%)	35 (7·3%)
Unknown	30 (12·7%)	35 (14·6%)	65 (13·6%)
AFP category			
≤10 ng/L	61 (25·7%)	69 (28·8%)	130 (27·3%)
11–400 ng/L	100 (42·2%)	110 (45·8%)	210 (44·0%)
>400 ng/L	76 (32·1%)	61 (25·4%)	137 (28·7%)
Portal-vein thrombosis			
Absent	181 (76·4%)	186 (77·5%)	367 (76·9%)
Partial	26 (11·0%)	26 (10·8%)	52 (10·9%)
Complete	13 (5·5%)	12 (5·0%)	25 (5·2%)
Unknown	17 (7·1%)	16 (6·7%)	33 (6·9%)
Tumour morphology			
Uninodular	109 (46·0%)	114 (47·5%)	223 (46·8%)
Multinodular	94 (39·7%)	96 (40·0%)	190 (39·8%)
Massive	20 (8·4%)	22 (9·2%)	42 (8·8%)
Unknown	14 (5·9%)	8 (3·3%)	22 (4·6%)
Involved liver volume			
≤50%	192 (81·0%)	194 (80·8%)	386 (80·9%)
>50%	40 (16·9%)	39 (16·3%)	79 (16·6%)
Unknown	5 (2·1%)	7 (2·9%)	12 (2·5%)
Type of local treatment			
None	128 (54·0%)	125 (52·1%)	253 (53·0%)
Liver transplantation	2 (0·8%)	1 (0·4%)	3 (0·6%)
Resection	11 (4·6%)	9 (3·7%)	20 (26·0%)
PEI	56 (23·6%)	68 (28·3%)	124 (26·0%)
TACE	37 (15·6%)	31 (12·%)	68 (14·3%)
Resection+PEI	1 (0·4%)	1 (0·4%)	2 (0·4%)
PEI+TACE	1 (0·4%)	5 (2·1%)	6 (1·3%)
Resection+PEI+TACE	1 (0·4%)	0	1 (0·2%)

PEI=percutaneous ethanol injection; TACE=transartherial chemoembolisation.
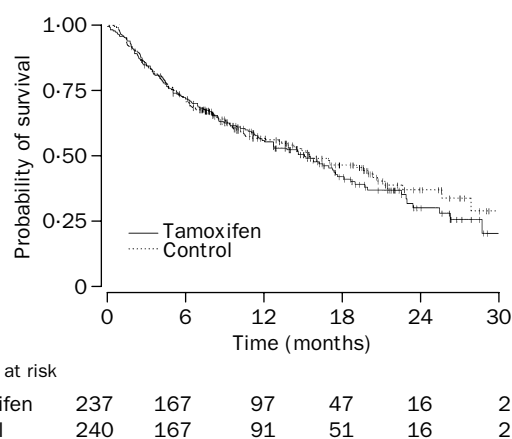
Table 2: **Characteristics of tumour**

Figure 2: **Kaplan-Meier estimated probability of survival**

Number at risk					
Tamoxifen	237	167	97	47	16	2
Control	240	167	91	51	16	2

cirrhosis. Most cases of viral cirrhosis were newly diagnosed with evidence of disease at entry into the trial. About half of them had well-compensated liver function.

Of 237 patients assigned tamoxifen, two (0·8%) never took the drug and 11 (4·6%) stopped taking it. Nine patients stopped taking tamoxifen because of toxicity and two because of refusal. Transplant-unit physicians stopped administration of tamoxifen in two patients after they had a liver transplantation. A further two patients stopped tamoxifen erroneously because of disease progression. Of 240 patients enrolled into the control arm, seven (2·9%) took tamoxifen.

23 (9·7%) patients allocated tamoxifen developed toxicity. Reported side-effects were: thrombophlebitis (one case), thrombocytopenia (two cases), hot flushes (three cases), itching (five cases), nausea (12 cases), and vomiting (five cases).

By Sept 15, 1997, 249 (52·2%) patients had died, 213 (44·7%) were alive at the end of the follow-up, and 15 (3·2%) were lost to follow-up. There was no significant effect (p=0·54) of tamoxifen on patients' survival (figure 2). Estimated median survival was 15 months and 16 months in the tamoxifen and the control arms, respectively. 1-year survival probability was 56% and 57%, respectively. In addition, no differences between tamoxifen and control arms were found within subgroups defined by prognostic variables (table 3). After adjustment for known prognostic factors, the relative hazard of death for patients receiving tamoxifen was 1·07 (95% CI 0·83–1·39).

	1-year survival (SE)		Median (SE) survival (months)		p*
	Tamoxifen	Control	Tamoxifen	Control	
All patients	56% (3)	57% (3)	15 (2)	16 (2)	..
Locoregional treatment					0·77
No	30% (5)	35% (5)	6 (1)	5 (1)	
Yes	74% (4)	70% (4)	23 (2)	22 (3)	
Child-Pugh categories					0·45
A	75% (5)	74% (5)	23 (4)	23 (2)	
B	43% (6)	51% (6)	9 (1)	12 (3)	
C	17% (8)	19% (7)	4 (1)	4 (1)	
Okuda categories					0·44
I	74% (4)	76% (5)	23 (3)	23 (2)	
II	40% (6)	43% (5)	9 (2)	9 (2)	
III	21% (9)	20% (10)	3 91)	4 (1)	

*First-order interaction with tamoxifen.

Table 3: **Efficacy of tamoxifen within subgroups defined by covariates in multivariate analysis**

First author [reference]	Number of patients	1-year survival (%)		Odds ratio (95% CI)
		Treated	Control	
Farinati [6]	38	22	5	3·84 (0·60–24·58)
Martinez-Cerezo [7]	36	48	9	7·42 (1·82–30·32)
Elba [8]	22	72	54	2·12 (0·39–11·56)
Castells [9]	120	51	43	1·29 (0·63–2·64)
Pooled four studies				*2·01 (1·14–3·55)*
CLIP-01 trial	477	55	56	0·97 (0·67–1·38)
Pooled five studies				*1·19 (0·88–1·61)*

Table 4: **Meta-analysis of trials comparing tamoxifen alone versus no active treatment in HCC**

Discussion

In this study, patients with HCC treated with tamoxifen had the same survival rate as patients who never took the drug. The patients entered in our study, mainly affected by viral cirrhosis, which is the most common condition underlying HCC in Italy,[13] were representative of patients with HCC seen in clinical practice. This was because of the broad eligibility criteria and the pragmatic approach (no placebo, no double-blinding, no strict follow-up rules, survival as the only end-point) that were applied. Our results may be generalised to all patients with HCC associated with viral cirrhosis and possibly to the whole population of patients with HCC.

Tamoxifen has been used in clinical practice for treatment of HCC since three studies[6–8] showed improved survival. These positive results were obtained despite a previous phase II study that did not show responses in patients with HCC treated with tamoxifen alone.[14] In 1995, Castells et al[9] in a double-blind placebo-controlled trial in 120 patients with advanced HCC, found that the survival of patients treated with tamoxifen was not significantly different from that of the placebo group. In 1997, a meta-analysis of clinical trials in HCC reported a significant survival advantage with tamoxifen at 1 year.[10]

All the above studies were done in very small series or in patients with HCC not amenable to any locoregional treatment because of advanced tumours or severe impairment of liver function, or both. Our study population was unselected for locoregional treatment and included a high proportion of patients with good liver function and small tumours (46% in the Child-Pugh A and 48% in the Okuda I categories). Our study was planned to show a more realistic survival advantage (11% at 1-year) for tamoxifen-treated patients than the Castells' hypothesis of 25% difference. Assuming an odds ratio of 2·0, from the meta-analysis, and a 1-year survival in the control group of 0·5, a survival advantage at 1 year of about 16% should be expected. To make our results consistent with previous publications, we also looked for possible survival differences within subgroups defined by prognostic factors (previous local treatment, degree of liver function, stage of the tumour), but we failed to find any significant effect of tamoxifen.

The results of this study changed the conclusion of the meta-analysis,[10] which we updated (table 4). The addition of our data to the four previous trials comparing tamoxifen alone versus no active treatment produced a pooled odds ratio of being alive at 1 year of 1·19 (95% CI 0·88–1·61).

Lack of tamoxifen efficacy could be ascribed either to low expression of oestrogen receptors in HCC[15] or to expression of mutated oestrogen receptors.[16] Accordingly, it could be proposed that the drug works well only in the subgroup of patients bearing functioning oestrogen receptors in their tumours. Our negative results, however,

suggest that either the effect of tamoxifen in this subset is negligible or this subgroup of patients is small.

In conclusion, the present study showed that tamoxifen was not effective in prolonging survival of patients with HCC.

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