UNIVERSITÀ DEGLI STUDI DI PALERMO

DOTTORATO DI RICERCA IN BIOPATOLOGIA

XXIII CICLO

NATURAL HISTORY OF HEPATOCELLULAR CARCINOMA AND EFFECTS OF TREATMENTS

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CHAPTER 1

INTRODUCTION

Hepatocellular carcinoma (HCC) is a major health problem. It is the sixth most common cancer worldwide and the third cause of cancer-related death. [1] In 2002 at least 600,000 new cases were registered and its incidence and prevalence in US and Western Europe have been increasing during the past decade. In 80% of cases HCC affects cirrhotic livers and it is now considered the first complication to occur and the major cause of liver-related death. [2] Principal risk factors for developing cirrhosis and then HCC are chronic liver diseases and in particular chronic B and C hepatitis/cirrhosis, alcoholic liver disease and nonalcoholic steatohepatitis-related cirrhosis. [3–5]

Guidelines for HCC management recommend mortality risk estimates as a decision-making support. [3] Unfortunately, the ability of all the available prognostic scores to predict mortality is far from perfect and none of these systems provide sufficient confidence for the prediction of the outcome in the individual patient with HCC. [3,6–8]

In the absence of an optimum prognostic model, treatment algorithms for patients with HCC in Europe and North America have been prepared on the basis of the Barcelona Clinic Liver Cancer (BCLC) classification. [3,9,10]

The BCLC staging classification for HCC classifies patients as having stages of disease from 0 to D (Figure 1).

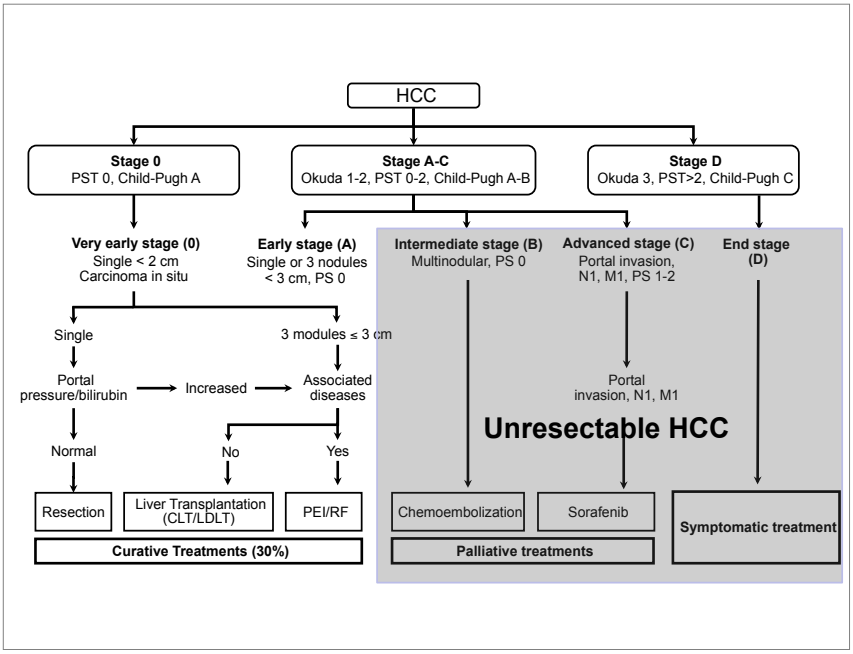

Figure 1 The Barcelona Clinic Liver Cancer staging system and treatment allocation. Abbreviations: CLT, cadaveric liver transplantation; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; PEI, percutaneous ethanol injection; RF, radiofrequency.

Stage 0 is very early disease, which is defined as a solitary liver cancer that measures ≤ 2 cm without tumor invasion into surrounding tissues.

Stage A is early disease, classified as patients who exhibit preserved liver function with a solitary HCC < 5 cm in size, or up to 3 tumors each of which is ≤ 3 cm in size. Patients with stage 0 or stage A disease can be effectively treated with curative therapies, such as surgical resection, liver transplantation, or by percutaneous ablation methods, including

percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA). With these treatments it is possible to obtain complete responses with potential long-term cure, as reflected by a 5-year survival better than 50% to 70%.

The BCLC intermediate stage (stage B) consists of asymptomatic patients with well-preserved liver function, and multinodular or large tumor extension, without macrovascular invasion or extrahepatic spread (ES). Patients with stage B (intermediate) disease treated with transarterial embolization (TAE) or transarterial chemoembolization (TACE) have demonstrated a significant increase in survival compared with best supportive care (median survival, 20 months vs 16 months). Patients with mild related symptoms and/or macrovascular invasion or ES are classified as advanced stage (BCLC stage C). Previously, no standard systemic therapy existed for the treatment of patients at this stage; however, two randomized controlled trials (RCTs) have now shown that sorafenib, an inhibitor of Raf kinase and vascular endothelial growth factor receptor (VEGFR), improves the overall survival of patients with stage C disease. Sorafenib is, therefore, now considered to be the standard treatment for advanced HCC. [11,12] Patients with cancer symptoms, related to progressed liver failure, tumor growth with vascular involvement, ES, or physical impairment (performance status > 2) are classified as stage D (end stage)

disease; they do not benefit from antitumor treatments and should receive only the best available supportive care.

It should be noted that not all patients defined by each stage of BCLC are ultimately candidates for the suggested treatment modality. For instance, TACE can be performed at an early stage in patients for whom RFA or PEI cannot be performed because of tumor location (proximity to a gallbladder, biliary tree, or blood vessel), or because of failed prior curative treatments or medical comorbidities. TACE is also the first-line therapy for downstaging tumors that exceed the criteria for transplantation or in patients awaiting orthotopic liver transplantation (OLT).

Moreover, even if guidelines for the management of HCC provide indications for the use of various treatments as mono-therapies, in clinical practice a multimodal approach that combines various techniques is used, either as first-line therapy or as a rescue (second-line) approach after the failure of a mono-therapy (Table 1). [13,14]

Table 1 The proposed purpose of combination therapy

Contextual	• Improved effectiveness over monotherapy for the treatment of single lesions • Improved effectiveness over monotherapy for the treatment of multiple lesions • Improved effectiveness over monotherapy for the prevention of tumor recurrence
Sequential	• Improved effectiveness over monotherapy for the treatment of large or difficult lesions • Rescue therapy after the failure of a first-line approach • Improved effectiveness over monotherapy for the prevention of tumor recurrence after complete response (adjuvant treatment) • To slow tumor progression for patients awaiting liver transplantation (bridge to transplant) • To reduce tumor size to meet orthotopic liver transplantation criteria (downstaging) • To allow for salvage transplantation in patients without proven malignant disease after liver resection if pathological findings (eg, evidence of vascular invasion) indicate the patient is at high risk of tumor recurrence ("salvage" transplantation)

Note. Modified from Cabibbo G, Latteri F, Antonucci M, Craxì A. Multimodal approaches to the treatment of hepatocellular carcinoma. Nat Clin Pract Gastroenterol Hepatol.2009;6(3):159–169. [14]

Prediction of Survival

Survival estimates are critical factors in physician and patient decision making, in all phases of neoplastic illness. Prognostic estimates in advanced cancer may have increased importance as patients near the end of life, since this is a natural time to formally reevaluate the goals of treatment, which may change from life prolongation to palliation.

However, despite its importance, prognostication in advanced cancer is imperfect. Physicians are typically optimistic in their estimates of patient survival, and the prognostic estimates they communicate to patients may be even more optimistic.

HCC is an insidious disease, with no particular or specific signs and symptoms of manifestation and whose behavior is usually unpredictable. Its natural history is also dependent on functional impairment of the underlying liver disease which often limits the application of therapeutic opportunities and influences survival.

The extensive application of surveillance programs for early detection of small (<5 cm) HCC has increased the number of tumors detected within the Milan criteria [15-17] at Barcelona Clinic Liver Cancer (BCLC) stages 0 or A (very early or early), and potentially responsive to curative treatments, such as liver transplantation and percutaneous or surgical ablation. [18]

Nonetheless, most patients with HCC (approximately 70%) are diagnosed at BCLC B (intermediate) and C (advanced) stages (approximately 50%) or BCLC D (end stage, approximately 20%). [18]

Clearly, for ethical reasons it is not possible to evaluate in RCTs the natural history of early HCC. However a milestone paper published in 1989 showed that 1- and 2-year overall survival of asymptomatic patients with HCC and cirrhosis was 96% and 50%, respectively. [19]

A previous systematic review [20] showed that the survival rates of untreated patients or of those who received placebo in randomized controlled trials (RCTs) of unresectable HCC vary among the studies, ranging from 10% to 72% at 1 year and from 8% to 50% at 2 years.

So, in the setting of unresectable HCC, an accurate estimate of survival among untreated patients is essential for (1) evaluating the natural history and assessing the validity of biological or radiological surrogate markers, (2) controlling for confounding factors in observational studies, (3) calculating the sample size and stratifying subjects in RCTs, and (4) assessing treatment effect size to formulate therapeutic strategies. In fact, knowledge of the factors influencing the outcome of untreated patients also may be important for interpreting the results of RCTs of different treatments.

Aim

According to all above presented evidences I aimed to further investigate, together with my group, the natural course of untreated patients with unresectable HCC.

CHAPTER
2

Natural History of Untreated Unresectable Hepatocellular Carcinoma

A Meta-Analysis of Survival Rates of Untreated Patients in Randomized Clinical Trials of Hepatocellular Carcinoma

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Knowing the spontaneous outcome of hepatocellular carcinoma (HCC) is important for designing randomized controlled trials (RCTs) of new therapeutic approaches; however, survival of patients in the absence of treatment is highly variable, and prognostic factors influencing outcomes are incompletely defined. The aims of this meta-analysis were to estimate the 1-year and 2-year survival rates of untreated HCC patients enrolled in RCTs of palliative treatments, and to identify prognostic factors. RCTs evaluating therapies for HCC with placebo or no-treatment arms were identified on MEDLINE through April 2009. Data were combined in a random effect model. Primary outcomes were 1-year and 2-year survival. Thirty studies met the inclusion criteria. The pooled estimates of the survival rates were 17.5% at 1 year (95% confidence interval [95%CI], 11%-27%; range, 0%-75%) and 7.3% at 2 years (95%CI, 3.9%-13%; range, 0%-50%). Heterogeneity among studies was highly significant ($P < 0.0001$) both for 1-year and 2-year survival, and persisted when RCTs were stratified according to all patient and study features. Through meta-regression, impaired performance status, Child-Pugh B-C class, and presence of portal vein thrombosis were all independently associated with shorter survival. Ascites was strongly linked to a worse outcome in intermediate/advanced Barcelona Clinic Liver Cancer stages. *Conclusion:* This meta-analysis confirms the heterogeneity of behavior of untreated HCC and provides a sound basis for stratifying patients with HCC according to expected survival in future trials of new anti-cancer agents. (HEPATOLOGY 2010;51:1274-1283.)

The extensive application of surveillance programs for early detection of small (<5 cm) hepatocellular carcinoma (HCC) has increased the number of tumors detected within the Milan criteria[1] at Barcelona Clinic Liver Cancer (BCLC) stages 0 or A (very early or early),[2] and potentially responsive to curative treatments, such as liver transplantation and percutaneous or surgical ablation.[3,4] Nonetheless, most patients with HCC (approximately 70%) are diagnosed at BCLC B (intermediate) and C (advanced) stages (approximately 50%) or BCLC D (end stage, approximately 20%).[4]

A previous systematic review[5] showed that the survival rates of untreated patients or of those who received placebo in randomized controlled trials (RCTs) of unresectable HCC vary among the studies, ranging from 10% to 72% at 1 year and from 8% to 50% at 2 years.

In the setting of unresectable HCC, an accurate estimate of survival among untreated patients is essential for (1) evaluating the natural history and assessing the validity of biological or radiological surrogate markers, (2) controlling for confounding factors in observational studies, (3) calculating the sample size and stratifying subjects in RCTs, and (4) assessing treatment effect size to formulate therapeutic strategies. Knowledge of the factors influencing the outcome of untreated patients also may be important for interpreting the results of RCTs of different treatments.

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; RCT, randomized controlled trial.

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Current guidelines for the management of HCC recommend mortality risk estimates as a decision-making support.[3] Although different palliative treatments (chemoembolization and recently, sorafenib) have been proposed for patients with HCC, prognosis remains poor. In BCLC B or C, the survival of treated patients is assumed to be 10% to 40% at 3 years.[6] In end-stage HCC (BCLC D), the prognosis is very poor, with a median survival of only 3 months.[4] Interpretation of the results of the RCTs of palliative treatments is problematic, with conflicting data, and there is no consensus for all HCC stages on the best algorithm of treatment, although chemoembolization and sorafenib are currently considered the standard of care for BCLC B and BCLC C stages, respectively.[6]

To resolve uncertainty by increasing the statistical power, we chose to do a meta-analysis of the placebo or inactive treatment arms of RCTs of palliative treatments for HCC, with the aims of (1) estimating the 1-year and 2-year rates of survival among patients receiving no treatment, or placebo; (2) analyzing the variability in survival rates by looking at the heterogeneity among the RCTs as a means of interpreting this variability; and finally, (3) identifying factors associated with a longer survival.

Patients and Methods

Selection of Trials. This analysis was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[7] The primary sources of the reviewed studies, exclusively in English, were MEDLINE, CANCERLIT, the Cochrane Controlled Trials Register, and the Cochrane Library, with the following medical subject headings (MeSH): *hepatocellular carcinoma*; *liver cancer*, *primary liver carcinoma*; *placebo*, *double-blind*; *therapy*; *treatment*; *chemoembolization*; *systemic therapy*; *randomized* or *randomised trial,* and *clinical trial*. The search included literature published through April 2009 with no lower date limit on the search results. The computer search was supplemented with manual searches for reference lists of all retrieved review articles, primary studies, and abstracts from meetings to identify other studies not found in the computer search. When the results of a single study were reported in more than one publication, only the most recent and complete data were included in the meta-analysis.

Studies were included in the analysis if (1) they were RCTs comparing any therapy with placebo, no treatment, or supportive care; (2) they included HCC patients with or without metastatic disease; (3) 1-year or 2-year survival was assessed as an outcome measure of the effect of the treatment; and (4) they had been published or accepted for publication as full-length articles.

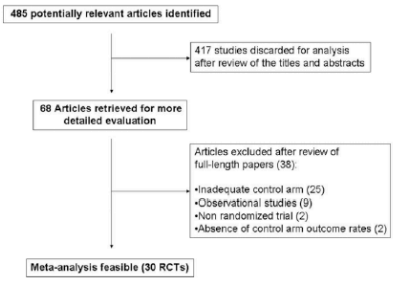

Fig. 1. Study flowchart.

Among the 485 studies reviewed (Fig. 1), 30 RCTs[8-37] met the inclusion criteria. Studies were excluded if they did not have an adequate control arm; if they were nonrandomized or if they enrolled randomized and nonrandomized patients; and if they were published only in abstract form. The rationale for excluding studies published as abstracts only was that the methodological quality could not be assessed.

Review of the Trials. The RCTs were reviewed using a list of predefined, pertinent questions that concerned the characteristics of patients, treatments, outcomes, and study validity. Each trial was evaluated and classified by three independent investigators (C.C., A.C., and G.C.). Discrepancies among reviewers were infrequent (overall interobserver variation of $<10\%$) and were resolved by discussion.

The methodological quality of the studies was assessed by five principal criteria (Supporting Table 1), using those established by Jadad et al.[38] and Bañares et al.,[39] as suggested by the Panel of Experts in HCC-Design Clinical Trials.[4] The quality of trials was evaluated according to each separate component. The maximum possible score was 10 points.

Statistical Analyses. Pooled estimates of 1-year and 2-year survival rates were calculated using random-effects logistic regression analysis after applying sample weights according to the sample size. Heterogeneity among studies was assessed with the Pearson chi-squared test. Three different methods were used to explore and explain the diversity among studies: (1) stratum analysis of variables suspected of having caused inconsistency, (2) meta-regression, and (3) subgroup analysis. Therefore, stratum-specific rates of the 1-year and 2-year survival rates for different patient-level and study-level covariates were cal-

culated. We used 16 stratifying variables: publication year, study validity, study location, mean age, percentage of males, percentage of alcohol-related liver disease, percentage of hepatitis B virus (HBV)–related liver disease, percentage of hepatitis C virus (HCV)–related liver disease, percentage of performance status 0 subjects, mean serum albumin, mean total bilirubin, prothrombin activity, percentage of solitary tumors, percentage of portal thrombosis, percentage of Child-Pugh A patients, and percentage of Okuda stage I patients.

Only univariate logistic regression analyses were used to examine the association between features of the study and the 1-year survival rates. We did not consider multivariate analysis because of the wide heterogeneity and lack of complete data for identification of possible variables that could explain heterogeneity. A chi-squared for interaction was used to examine whether the 1-year survival varied significantly between subgroups.

Begg's funnel plots were generated, and Egger's regression asymmetry test was used to examine potential publication bias related to the 1-year survival rates. For all analyses, $P < 0.05$ was considered statistically significant. All analyses were completed with SAS version 8.1 (SAS Institute, Cary, NC) software.

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Results

Description of the Studies. After review of the titles and abstracts, 30 RCTs[8-37] fulfilled the inclusion criteria and were selected for review. Twenty studies[9,12-21,23,25,26,28,31,33-35,37] were North American and European, and 10[8,10,11,22,24,27,29,30,32,36] were Asian-Pacific. Of the 30 RCTs, 14[8-21] were published before 2000, and the other 16[22-37] since 2000. The distribution of the main characteristics of patients in the control arm of the 30 RCTs[8-37] considered in the current analysis is reported in Table 1. Characteristics of arms (treatment and control) of RCTs included in the meta-analysis are detailed in Supporting Table 2. In 15 RCTs, there was an inactive placebo arm,[12,15-17,19,24,25,29,30,32-37] whereas in the others, untreated patients received no treatment or supportive care only.[8-11,13,14,18,20-23,26-28,31]

A total of 4335 patients were included in these 30 studies, 1927 of whom were in the control group. The size of the control groups in each study ranged from 11[12] to 303[35] patients. The percentage of men ranged from 65[26] to 100.[11] Mean patient age was 62.3, ranging from 49[11] to 69.[34,37] The proportion of patients with cirrhosis ranged from 63[34] to 100%.[12,19,20,23]

Data on the cause of liver disease were missing in many trials. HCV status was not reported in 11 trials,[8-12,17,22,24,27,30,37] and anti-HCV, when reported, was positive in 4[36] to 94%[13] of the patients. HBV status was not reported in six trials,[9,11,12,22,30,37] and hepatitis B surface antigen, when reported, was positive in 0[13,23] to 94.4%.[10] The proportion of patients with alcohol-related liver disease was not reported in 13 RCTs,[8,10-12,18,22,24,26,27,30,32,34,36] and ranged from 2.5[25] to 78%[31] in studies reporting alcohol consumption.

Among the studies providing data on the distribution of the ECOG Performance Status (ECOG PS),[13,16,17,20,27,28,30,31,32,35-37] the frequency of an ECOG PS = 0 went from 0[32] to 77%.[28] Information on the presence of ascites was missing from most trials[8,11,12,14,15,17-19,21,22,24,25,27,29,30,33-37] and ranged from 8%[26] to 63%[16] in the studies reporting it. Mean albumin levels were comparable in the RCTs, ranging from 3 g/dL[26] to 4 g/dL.[35] Mean bilirubin levels differed greatly among RCTs, ranging from 0.7 mg/dL[35] to 6.6 mg/dL.[18]

Only 13 RCTs[14,16,18-21,23,25,27-29,33,34] provided information about the tumor pattern at diagnosis (solitary versus multinodular/diffuse). Solitary tumor rates varied greatly, ranging from 0[34] to 57%.[18] The proportion of patients with portal vein thrombosis was reported in 20 studies[9,13,14,16,19-23,25-29,31,33-37] and differed greatly among the trials, ranging from 0[9,20,28,34] to 65%.[22]

Methodological quality scores ranged from 4[12,32] to 10[33,35,36] on a scale of 2 to 10 (Supporting Table 3). With regard to the quality of the studies, all trials except one[30] reported an adequate efficacy of randomization, and only five studies[12,13,19,24,32] did not report an adequate follow-up. Adequate blinding was used in eight RCTs.[15-17,19,30,33,35,36] Twenty-three trials (77%) showed a high-quality score (≥6 points).[8-11,14-21,23,26-30,33-37]

Survival Rates. The pooled estimate of the 1-year survival rate was 17.5% (95% confidence interval [CI], 11%-27%; range, 0-75%). There was a statistically significant heterogeneity among studies, $P < 0.0001$ (Fig. 2).

Logistic regression analysis was used to identify potential sources of heterogeneity among the studies. Using the univariate logistic regression, of the 16 variables assessed only nine were associated with an increase in the 1-year survival rate: North American and European studies ($P = 0.001$), female sex ($P = 0.043$), low percentage of hepatitis B surface antigen–positive patients ($P = 0.001$), high percentage of ECOG PS = 0 patients ($P = 0.001$), high albumin level ($P = 0.038$), high prothrombin activity ($P = 0.001$), low percentage of portal vein thrombosis ($P = 0.001$), high percentage of Child-Pugh class A patients ($P = 0.042$), and high percentage of Okuda stage I patients ($P = 0.001$) (Table 2).

Table 1. Characteristics of Untreated, or Treated with Placebo, Patients in RCTs of Hepatocellular Carcinoma

Author	Year	Sample*	Centers	Regions†	Mean Age	Male Sex (%)	Etiology (%) Alcohol/HCV/HBV	Prothrombin Activity (%)	Albumin	Bilirubin	Ascites (%)	C-P Class A/B/C (%)	PT (%)	AFP	ECOG PS 0/1/2 (%)	Solitary %	Okuda Stage I/II/III (%)	Survival (%) 1 Year	Survival (%) 2 Year
Lai et al.[8]	1988	46	1	2	57	82	NA/NA/67.3	NA	NA	1.8	NA	NA	NA	800	NA	NA	NA	3.5	0
Pelletier et al.[9]	1990	21	1	1	66	86	85.7/NA/NA	76	3.3	2.3	57	NA	0	1983	NA	NA	24/52/24	24	NA
Lai et al.[10]	1993	36	1	2	60	81	NA/NA/94,4	NA	NA	1.1	19	NA	NA	NA	NA	NA	NA	3.3	0
Madden et al.[11]	1993	25	1	2	49	100	NA/NA/NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	0
Elba et al.[12]	1994	11	1	1	64	73	NA/NA/NA	NA	NA	NA	NA	82/18/0	NA	NA	NA	NA	27/73/0	47	10
Martinez Cerezo et al.[13]	1994	16	1	1	65	81	50/94/0	NA	3.5	2.4	44	44/38/18	12	NA	37.5/56.2/6.3	NA	NA	9,1	NA
GRETCH[14]	1995	46	24	1	65	96	73/10/7	75	3.8	1.4	NA	NA	13	92	NA	30	NA	43.5	26
Manesis et al.[15]	1995	29	1	1	62	79	22/20/58	52	NA	NA	NA	NA	NA	NA	NA	NA	24.1/59/17.2	0	NA
Castells et al.[16]	1995	62	1	1	65	69	8.1/74/6	76	3.6	1.8	63	NA	39	NA	46.8/43.5/9.7	24	45/55/0	43	29
Grimaldi et al.[17]	1998	59	multi	1	NA	78	39/NA/35	NA	NA	NA	NA	NA	NA	NA	26/58/17	NA	NA	36.6	11.6
Kouroumalis et al.[18]	1998	30	NA	1	68	83	NA/53/27	NA	3.2	6.6	NA	6/38/56	NA	NA	NA	57	10/33/57	13	NA
Riestra et al.[19]	1998	37	4	1	65	78	27/29.7/8.1	77	NA	2	NA	NA	22	NA	NA	35	43/43/14	37.8	NA
Bruix et al.[20]	1998	40	1	1	64	75	2.5/77/2.5	79	3.5	1.5	18	NA	0	NA	67.5/27.5/5	27,5	67.5/32.5/0	75	50
CLIP Group[21]	1998	240	30	1	67	76	2.5/78.1/11.4	73	3.5	1.9	NA	44/36/15	15,8	NA	NA	47,5	42.1/37.5/5.8	57	37
Chung et al.[22]	2000	26	1	2	53	NA	NA/NA/NA	NA	NA	NA	NA	46/42/12	65	NA	NA	NA	NA	0	0
Llovet et al.[23]	2000	28	multi	1	63	78	18/78/0	84	3.5	1.4	61	NA	39	NA	NA	36	28.6/71.4/0	36	12
Liu et al.[24]	2000	58	1	2	60	95	NA/NA/81	NA	NA	1.8	NA	48/36/16	NA	1,377	NA	NA	10.3/67.2/22.4	0,0	0
Villa et al.[25]	2001	24	1	1	60	92	0/62.5/37.5	77	3.1	1.7	NA	42/29/29	17	NA	NA	54,2	NA	29	15
Ishikawa et al.[26]	2001	20	1	1	61	65	NA/85/15	56	3	2.3	8	20/65/15	40	NA	NA	NA	20/60/20	5.5	0
Lo et al.[27]	2002	39	1	2	63	87	NA/NA/74	NA	3.7	0.8	NA	NA	31	NA	35.9/48.7/15.4	38	46.2/53.8/0	32	11
Llovet et al.[28]	2002	35	3	1	66	66	3/91/3	77	3.5	1.5	31	60/40/0	0	NA	77/11.5/11.5	23	62.8/37.2/0	63	27
Yuen et al.[29]	2002	35	1	2	62	94	2.8/5.7/66	NA	3.2	1.4	NA	34/63/3	60	721	NA	54	8.6/74.3/17.1	0	0
Chow et al.[30]	2002	130	10	2	60	82	NA/NA/NA	NA	NA	NA	NA	40/48/12	NA	NA	19/45/36	NA	11/69/20	12	5
Barbare et al.[31]	2005	210	78	1	67	90	78/11/6	NA	NA	NA	35	50/44/4	37,4	NA	14.8/53.3/31.9	NA	35/57/8	19.9	6
Sarin et al.[32]	2006	19	NA	2	52	79	NA/15.8/78.9	NA	3.5	2.2	53	32/68/0	NA	NA	0/NA/NA	NA	0/100/0	15.8	5.3
Becker et al.[33]	2007	59	7	1	67	85	52/16/10	NA	NA	NA	NA	53/37/10	44	NA	NA	21	32/58/10	25	15.6
Dimitroulopoulos et al.[34]	2007	30	1	1	69	73	NA/57/10	NA	NA	NA	NA	27/63/0	0	3208	NA	0	NA	3	0
Llovet et al.[35]	2008	303	121	1	66	87	26/27/55	NA	4	0.7	NA	98/2/0	41	99	54/39/7	NA	NA	33	NA
Cheng et al.[36]	2009	76	23	2	52	66	NA/4/78	NA	NA	NA	NA	97/3/0	34	NA	27.6/67.1/5.3	NA	NA	17.5	NA
Barbare et al.[37]	2009	137	79	1	69	69	74/NA/NA	NA	NA	NA	NA	67/23/0	23	NA	PS0-1% 80	NA	NA	30	14

*Control arm sample.

†For regions, 1 corresponds to North American and European studies; 2 to Asia-Pacific studies.

HCV, hepatitis C virus; HBV, hepatitis B virus; C-P, Child-Pugh; PT, portal vein thrombosis; AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group–performance status.

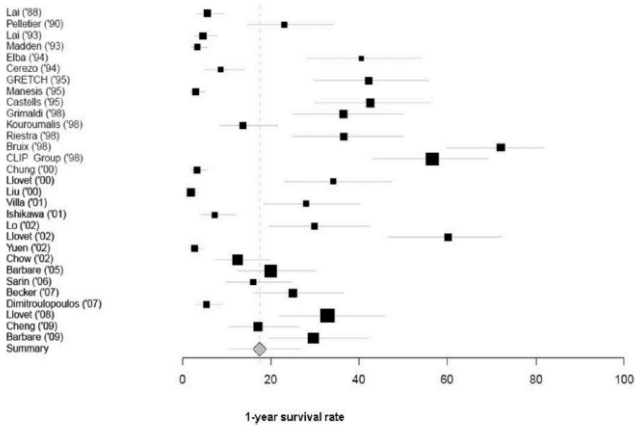

Fig. 2. Forest plot of 1-year survival rates of the placebo or untreated arms of 30 RCTs using random-effects model. Studies are arranged by publication year.

To assess any differences causing heterogeneity within each stratum of relevant study features, we calculated the pooled estimates of the 1-year survival rate within each stratum and evaluated heterogeneity among strata. However, heterogeneity was equally evident in all strata (Supporting Table 4).

The pooled estimate of the 2-year survival rate was 7.3% (95%CI, 3.9%-13%; range, 0-50%). Again, there was a statistically significant heterogeneity among studies ($P < 0.0001$) (Fig. 3).

Subgroup Analyses. Subgroup analyses were performed to evaluate whether the 1-year survival was differ-

Table 2. Predictors of 1-Year Survival Among All Studies

Study Characteristics	Outcome (1-Year Survival)				
	No. of studies	No. of patients	β	SE	P
Publication year	30	1927	0.03	0.05	0.487
Study validity	30	1927	0.21	0.17	0.228
Study location* (2 versus 1)	30	1927	−2.01	0.52	0.001
Male sex, %	29	1901	−0.06	0.03	0.043
Cause of liver disease					
Alcohol, %	17	1381	−0.01	0.01	0.413
HCV, %	19	1339	0.01	0.01	0.131
HBV, %	24	1577	−0.02	0.01	0.001
ECOG PS 0,† %	12	1126	0.03	0.01	0.001
Albumin, g/dL	15	958	2.34	1.13	0.038
Bilirubin, mg/dL	19	1135	−0.19	0.31	0.533
Prothrombin activity, %	11	582	0.13	0.03	0.001
Presence of ascites, %	10	487	−0.01	0.02	0.569
Tumor stage					
Solitary, %	13	705	−0.01	0.02	0.699
Multinodular/massive, %	13	705	0.01	0.02	0.699
Portal vein thrombosis, %	20	1484	−0.03	0.01	0.001
Child-Pugh class A, %	18	1459	0.02	0.01	0.042
Okuda stage I, %	18	1103	0.06	0.01	0.001

*For study location, 1 corresponds to North American and European studies; 2 to Asia-Pacific studies.
†Eastern Cooperative Oncology Group–performance status.
HCV, hepatitis C virus; HBV, hepatitis B virus; SE, standard error.

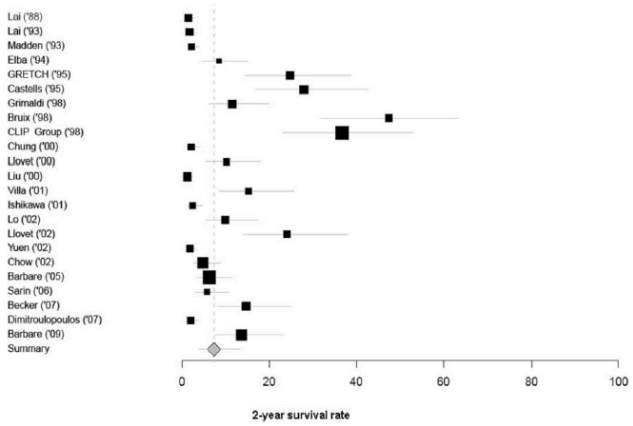

Fig. 3. Forest plot of 2-year survival rates, using random-effects model, in the placebo or untreated arms of 23 RCTs. Studies are arranged by publication year.

ent according to the various BCLC stages. Because BCLC classification was specifically reported only by a minority of studies,[23,28,32,34,35,36] we extrapolated from RCTs that provided information on Child-Pugh class or Okuda stage [9,12,13,15,18-30] so that patients belonging to Child-Pugh class C or to Okuda stage III could be considered BCLC D stage. Thus, according to the BCLC classification, we separated RCTs including only intermediate (B) and advanced (C) BCLC patients (named B+C stage studies) from those that also included patients in the end-stage D (named D stage studies).

The pooled estimate of BCLC B+C stage 1-year survival rate was 34% (95%CI, 22-48; range, 3%-75%). There was a statistically significant heterogeneity among studies, $P < 0.0001$ (Fig. 4A).

The pooled estimate of BCLC B stage 1-year survival rate was 49.6% (95%CI, 32-75; range, 3%-75%). There was a statistically significant heterogeneity among studies, $P < 0.0001$ (Supporting Fig. 1A).

The pooled estimate of BCLC C stage 1-year survival rate was 25% (95%CI, 14-40; range, 3%-63%). There was a statistically significant heterogeneity among studies, $P < 0.0001$ (Supporting Fig. 1B).

The pooled estimate of BCLC D stage 1-year survival rate was 11% (95%CI, 4.7-22; range, 0-57%), and there was a statistically significant heterogeneity among studies, $P < 0.0001$ (Fig. 4B).

We in turn excluded each study to ensure that no single study would be solely responsible for the heterogeneity of any result (so-called robust analysis). In all the robust analyses, heterogeneity among studies was significant. Moreover, in all the sensitivity analyses excluding the 2 RCTs with the highest and the lowest survival rates, heterogeneity was significant.

Regression analysis for the B+C stage studies showed that six variables were associated with an increased 1-year survival rate: studies published before 2000 ($P = 0.001$), low prevalence of alcohol-related disease ($P = 0.016$), high prevalence of HCV-related disease ($P = 0.021$), high percentage of ECOG PS = 0 patients ($P = 0.001$), low percentage of patients with ascites ($P = 0.001$), and high percentage of Okuda stage I patients ($P = 0.001$) (Table 3).

Regression analysis for the D stage studies showed that three variables were associated with an increased 1-year survival rate: North American and European studies ($P = 0.006$), low percentage of HBV-related disease ($P = 0.004$), and low percentage of portal vein thrombosis ($P = 0.01$)

To examine any potential differences in study features, we next calculated pooled estimates of the 1-year survival rate within each stratum and evaluated heterogeneity among strata. However, heterogeneity was equally evident in all strata (Supporting Table 5).

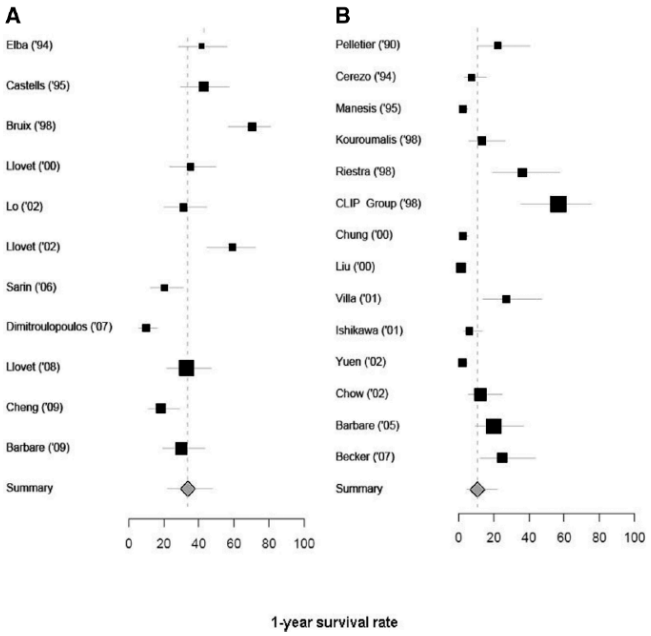

Fig. 4. Forest plot of 1-year survival rates, using random-effects model, of B+C stage studies (A), and Forest plot of 1-year survival rates, using random-effects model, of D stage studies (B) in the placebo or untreated arms. Studies are arranged by publication year.

Publication Bias. The funnel and the Egger publication bias plots for 1-year survival rates are shown in Supporting Fig. 2. The plots and the Egger test for publication bias showed that the risk of having missed or overlooked trials was significant: the *P* value was 0.0003 with the Egger test.

The funnel and the Egger publication bias plots for 2-year survival rates are shown in Supporting Fig. 3. The plots and the Egger test for publication bias showed that the risk of having missed or overlooked trials was significant: the *P* value was 0.003 with the Egger test.

Discussion

The survival rate in the placebo or untreated arm of RCTs of HCC patients may be a reliable measure of the spontaneous course of disease and a basic measure for both calculating sample size and providing a better prognostic stratification in RCTs evaluating new drugs or new multimodal approaches in the palliative setting. Until recently, new agents for patients with advanced HCC (BCLC stage C) were usually compared with either placebo or best supportive care. Recently, sorafenib was shown to significantly improve overall survival in two double-blind phase 3 RCTs,[35,36] although other anti-angiogenic agents are currently being compared alone or in combination. Most investigators and clinicians are now accepting sorafenib as the standard of care, and an expert panel has recommended it as a standard of care control arm for future RCTs of first-line systemic agents,[4,6] if the new agents are detected to have a powerful signal in phase 1 or 2 investigations.[40] As a result, it will be unfeasible to design future trials with an untreated control arm. The 1-year overall survival rate of 34% obtained in this meta-analysis in intermediate/advanced untreated controls can be considered a useful reference value for determining the sample size of future studies and for obtaining indirect

Table 3. Predictors of 1-Year Survival Among B+C Stage Studies

Study Characteristics	Outcome (1-Year Survival)				
	No. of studies	No. of patients	β	SE	P
Publication year	11	780	−0.08	0.02	0.001
Study validity	11	780	0.03	0.83	0.686
Study location* (2 versus 1)	11	780	−2.92	0.60	0.124
Male sex, %	11	780	−0.01	0.04	0.787
Cause of liver disease					
Alcohol, %	6	605	−0.01	0.01	0.016
HCV, %	8	593	0.02	0.01	0.021
HBV, %	9	632	−0.01	0.01	0.097
ECOG PS 0,† %	8	711	0.03	0.01	0.001
Albumin, g/dL	7	526	−1.43	1.45	0.316
Bilirubin, mg/dL	7	526	0.03	0.61	0.960
Prothrombin activity, %	4	165	−0.07	0.10	0.473
Presence of ascites, %	5	184	−0.03	0.01	0.001
Tumor stage					
Solitary, %	6	234	0.06	0.03	0.102
Multinodular/massive, %	6	234	−0.06	0.03	0.102
Portal vein thrombosis, %	9	750	−0.01	0.01	0.536
Child-Pugh class A, %	7	611	0.01	0.01	0.224
Okuda stage I, %	7	234	0.03	0.01	0.001

*Study location 1 corresponds to North American and European studies; 2 to Asian-Pacific studies.
†Eastern Cooperative Oncology Group–performance status.
HCV, hepatitis C virus; HBV, hepatitis B virus; SE, standard error.

comparisons among different trials estimating drug efficacy. The 1-year survival observed in the control arm of the SHARP RCT[35] was comparable (35%) to that estimated in this meta-analysis, but much higher than that observed in the Asian Pacific sorafenib study (17.5%).[36] While underlining the external validity of the results of this meta-analysis, this difference prompts a specific warning against generalizing results to all patient settings. Indirect comparison among trials assessing different drugs is to be discouraged because the different estimates of drug efficacy could be entirely related to the different baseline risks of the populations studied.

This meta-analysis of aggregated data from the placebo or untreated arms of 30 RCTs of palliative treatment in HCC clearly demonstrates that the heterogeneity of 1-year and 2-year survival is a common feature of these studies. There were significant differences between the studies, with observed survival rates ranging from 0%-75% at 1 year and from 0%-50% at 2 years. In our analysis, the pooled survival rate estimated by the random effects model was 17.5% at 1 year and 6.9% at 2 years. Although the number of included patients in the available studies was large, suggesting robustness of the estimated survival rates, the confidence intervals of the estimates at 1 year (95%CI, 11%-27%) and 2 years (95%CI, 3.5%-13%) remain wide. This inconsistency among RCTs of palliative treatments for HCC is not surprising if one considers all potential biases in the selection of patients with different demographic and clinical characteristics, different timing of referral and diagnostic criteria, true differences in case mix, cause, severity of the underlying cirrhosis, and tumor burden in terms of number and size of HCC nodules and of presence of macrovascular invasion or extrahepatic spread. An attempt to explain the wide variability in the natural course of eligible to palliative treatment of HCC was made by stratifying studies according to variables that described the patients studied and the study design features. However, a significant heterogeneity in survival among RCTs remained even after stratifying patients and study features, and heterogeneity in the survival rates persisted even in the stratum of high-quality studies, implying that this was not explained by study validity alone. Therefore, the evaluation of the methodological quality did not seem to influence the variability of the assessed outcome, because of the mean high quality of the studies (75% of these RCTs were high-quality studies). Heterogeneity of these rates among RCTs may reflect both inclusion of patients with different stages of disease and variability in the molecular characteristics and biological behavior of the tumor, which are not included in any of the currently available staging systems.

In our analysis, when studies were separated according to the BCLC stage, the 1-year survival was much higher in RCTs including only BCLC B or C patients (34%) than in those also including BCLC D patients (11%). This provides further evidence that the BCLC staging system has a good discriminative capacity for prognosticating

survival not only in patients with early HCC[41] but also in those with intermediate/advanced HCC. However, data on direct BCLC stage were lacking in several trials, and caution must be exercised when interpreting results from subgroup exploratory analyses. We found by meta-regression analysis that ECOG performance status and portal vein thrombosis are robust predictors of death in untreated patients as reported by Tandon and Garcia-Tsao[42] in a recent systematic review of 72 studies on prognostic indicators in HCC. These two individual parameters, both included in the BCLC classification, may explain in large part why this staging system provides accurate information on prognosis in the setting of HCC.

A remarkable difference in survival was found between occidental (North American and European) and oriental (Asia-Pacific) studies. The high prevalence of HBV-related liver disease found in Asia-Pacific countries may account for the different survival observed between oriental and occidental studies in which a high prevalence of HCV-related liver disease was observed. However, the potential role of HBV as a prognostic factor disappears when Asian-Pacific location of the studies and HBV-related disease were both included in a multivariate model.

The survival differences between occidental and Asian studies may be explained by differences in the distribution of other risk and prognostic factors. In fact, the worse survival observed in the Asia-Pacific study[36] could be explained by the higher prevalence of patients in advanced stage than in the SHARP study.[35]

Subgroup analysis of RCTs including only patients in BCLC intermediate (B) or advanced (C) stages provides further evidence that clinically detected ascites is strongly linked to poor survival. The prognostic value of ascites determines the importance of subclassifying the intermediate stage in relation to the therapeutic option. We believe that the benefits of transarterial chemoembolization (TACE) may outweigh the risks for BCLC B patients with Child-Pugh class A or B cirrhosis without ascites, whereas the risks may outweigh the benefits for BCLC B patients with Child-Pugh class A or B cirrhosis with ascites. Recently, in the subgroup analysis of the SHARP RCT,[43] based on BCLC stages, a trend for overall survival benefit was found in patients with BCLC B stage disease treated with sorafenib. However, the small sample size may have affected the study's ability to achieve statistical significance. Further large studies of BCLC B intermediate stage that stratify Child-Pugh class B patients according to ascites are needed to avoid overtreatment by TACE and to confirm the benefit of sorafenib in patients with BCLC B stage.

We found a significant difference in the pooled survival rates among the strata. In particular, studies published before 2000 showed a 1-year survival rate higher than studies published after 2000, perhaps indicating the inclusion of a high number of patients in advanced stages in recent years.

The meta-analysis was performed using summary data, and more detailed comparisons of survival could be made with a meta-analysis of individual patient data. However, it may not always be possible to obtain individual patient data from all the studies, raising the issue that the studies for which data are available may represent a biased subset of the available studies. As with all meta-analyses, the methodology of the current study results in a potential limitation of the generalizability of its results to new populations and settings, because these were obtained in small RCTs performed in highly specialized centers. Furthermore, our study is limited by the patient-level covariates reported in each of the studies, which are not consistent across trials, representing a further source of heterogeneity.

Lack of data on other potential confounders, such as microscopic vascular invasion, histological grading, and gene profiling, also could affect the accuracy of the results.

Finally, we should be especially concerned about publication bias in settings in which many small studies are being conducted. The risk of having missed or overlooked trials in the setting of studies assessing mortality in patients with HCC was substantial. Therefore, it is likely that small studies with a low rate of mortality or small drug (or new treatment) effect remain preferentially unpublished. However, the single large placebo-controlled trial,[44] still unpublished as a full paper, reported 1-year and 2-year survival rates similar to that given in this meta-analysis.

In untreated HCC patients, the available evidence is sufficient to conclude that (1) the 1-year and 2-year survival is extremely variable, and no single patient or study characteristic can explain this heterogeneity; (2) bad performance status, Child-Pugh B-C classes, and presence of portal vein thrombosis are associated with a worse prognosis; and (3) the presence of ascites is associated with poor survival in intermediate/advanced BCLC stages.

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CHAPTER
3

Treatment of Unresectable Hepatocellular Carcinoma

3.1 Transarterial chemoembolization

The observation that the majority of the blood supply to HCCs is derived from the hepatic artery has led to the development of techniques designed to eliminate the tumor's blood supply or to administer cytotoxic chemotherapy directly to the tumor. Transarterial chemoembolization (TACE) involves the injection of a chemotherapeutic agent, with or without lipiodol or a procoagulant material, into the hepatic artery. Lipiodol is an oily contrast agent that promotes intratumoral retention of chemotherapy drugs. A more recent method of chemoembolization involves the use of drug-eluting polyvinyl alcohol microspheres (“beads”), which seems to cause less toxicity with similar efficacy. Simultaneous or sequential occlusion of the hepatic artery until stagnation of blood flow to the tumor occurs may result in greater antitumor efficacy than chemotherapy alone.

TACE is the most widely used first-line treatment in the Western world and Asia for patients with unresectable HCC and has been shown to improve survival among patients with preserved liver function, particularly those with Child–Pugh class A cirrhosis who do not have extrahepatic metastases, vascular invasion, or prominent cancer-related symptoms. Two published meta-analyses of randomized, controlled trials assessing the use of arterial embolization, chemoembolization,

or both as primary palliative treatment for hepatocellular carcinoma showed that these procedures were associated with an improved 2-year survival rate as compared with conservative treatment. [20,21]

Interpretation of the results of these meta-analysis is also difficult because previous studies with TACE were not standardized for embolization procedures while recent developments with TACE, including new, more effective embolizing agents, [22] make standardization better, thus requiring a redefinition of selection criteria and endpoints in TACE studies.

TACE is also used as a neoadjuvant therapy or as a means of downstaging a patient's condition before liver transplantation, but whether these approaches provide a survival benefit is unclear. A post-embolization syndrome of fever and abdominal pain related to hepatic ischemia occurs in up to 50% of patients treated with TACE. There are few data to guide the choice of the chemotherapeutic agent or the retreatment schedule, which in practice ranges from 2 to 5 sessions. In recent randomized, controlled trials, [23,24] the use of a drug-eluting bead that releases the drug in a controlled fashion during TACE has been shown to be associated with a reduction in both hepatic and systemic side effects and with an increase in local tumor response.

Aim

According to all above presented evidences I aimed to further explore, together with my group, predictors of survival in patients with HCC receiving TACE as first line or second-line treatment.

AP&T Alimentary Pharmacology and Therapeutics

Predicting survival in patients with hepatocellular carcinoma treated by transarterial chemoembolisation

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SUMMARY

Background
Transarterial chemoembolisation (TACE) is first-line treatment in unresectable hepatocellular carcinoma (HCC) and rescue treatment after failure of radical treatments in early stage HCC. Prognostic tools for HCC using time-fixed Cox models may be unreliable in patients treated with TACE because time-varying predictors interact.

Aim
To explore time-dependent variables as survival predictors in patients with HCC receiving TACE as first-line or second-line treatment.

Methods
Eighty four consecutive patients with HCC (mean age 68; male gender 62%; Child-Pugh class: A $n = 73$, B $n = 11$; Barcelona Clinic Liver Cancer class: A $n = 44$, B $n = 24$, C $n = 16$) treated with TACE were enrolled. Clinical, laboratory and radiological follow-up data were collected from the time of first treatment. Time-fixed and time-dependent Cox analyses were done.

Results
Overall survival rates were 89.6% (95% CI 82.5–97.2) at 12 months, 58.8% (95% CI 46.2–74.9) at 24, 35.4% (95% CI 22.3–56.1) at 36 and 17.2% (95% CI 7.0–41.7) at 48 months. Performance status ($P < 0.001$), number of nodules ($P < 0.016$) and prior therapy ($P = 0.017$) were the only variables strongly linked to survival by time-fixed Cox model. Performance status ($P < 0.001$), prior therapy ($P = 0.005$), number of treatments ($P = 0.013$), complete response after TACE ($P = 0.005$) and bilirubin level ($P < 0.001$) were associated with survival using a time-dependent Cox model.

Conclusions
Survival after TACE is influenced most by performance status, complete response and bilirubin. Compared with the time-fixed models, a time-dependent Cox model has the potential to estimate a more precise prognosis in HCC patients treated with TACE.

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INTRODUCTION

Transarterial chemoembolisation (TACE) is the most widely used first-line treatment in the Western world and Asia for patients with unresectable hepatocellular carcinoma (HCC). TACE is considered the standard of care in these patients on the basis of two published meta-analyses that cleared demonstrated 2-year overall survival benefit.[1, 2] There is sufficient evidence from randomised controlled trials (RCTs) on the type of patients who are candidates for TACE. In addition, the American Association for the Study of Liver Diseases (AASLD) Practice Guideline for the management of HCC indicates TACE in nonsurgical patients at intermediate Barcelona Clinic Liver Cancer (BCLC) B stage.[3] Nonetheless, application of TACE in real clinical practice remains a matter of debate.

The selection criteria used to identify the candidates for TACE vary nationally and internationally.[2] Optimal candidates are patients with excellent liver functional reserve who are not presented with cancer-related symptoms or vascular invasion.[3, 4] However, intermediate BCLC B patients may have ascites, which is strongly linked to poor survival in this stage.[5, 6] Moreover, TACE can be performed in early-stage (BCLC A) patients for whom percutaneous radiofrequency thermal ablation (RFTA) is not feasible because of tumour location (proximity to gall-bladder, biliary tree, or blood vessel) or on whom surgery cannot be performed because of comorbidities.[7]

Despite the many RCTs that have been done to identify the optimal chemoembolisation procedure, lack of standardisation affects some aspects of treatment, including embolisation technique and treatment schedules.[8, 9] A relevant clinical question is whether patients should receive repeated courses of TACE at fixed intervals until the planned numbers of courses is reached or until a complete radiological response is achieved. There is no evidence that complete radiological response after TACE is a surrogate end-point strongly linked to overall survival.

A major problem in assessing overall survival of patients with HCC secondary to cirrhosis arises from a lack of accurate models able to predict outcome in the individual patient.[3, 10–12] Two factors may contribute to a less than satisfactory performance.

First, all previous prognostic models were general, not specialised, models for evaluating patient outcomes within specific populations or allocation treatment groups (e.g. liver transplantation, percutaneous ablation, TACE and systemic therapies).

Second, all the previous prognostic models assumed that the variables noted at one single time point for each patient were sufficient for predicting survival. In HCC, as in most chronic diseases, the clinical situation changes with time, particularly after a treatment. Conceivably, the weight of prognostic indicators changes in different phases of the disease, and estimates of prognosis could improve if such time-dependent changes were taken into account.

The aims of this prospective cohort study of HCC patients treated with TACE as first-line or second-line treatment were:

(i) to assess the effectiveness of TACE in HCC patients;

(ii) select the optimal candidate for TACE by identification of predictors of overall survival; and

(iii) improve the accuracy of mortality risk estimates with a new prognostic model that accounts for changes during the course of the disease.

MATERIALS AND METHODS

Patients

From January 2004 to May 2009, 84 consecutive HCC patients were treated with TACE as first-line or second-line treatment at our institution. Follow-up was censored on 31 October 2009. HCC was diagnosed and staged, respectively, according to AASLD criteria and BCLC schedule.[3]

Patients with early tumours (single tumours measuring less than 5 cm, or three nodules measuring less than 3 cm) were considered for curative therapies. Resection was indicated for patients with single tumours, absence of portal hypertension and normal bilirubin concentrations. Patients with portal hypertension or abnormal bilirubin concentrations or three nodules of less than 3 cm in diameter were considered for transplantation. Percutaneous treatment was performed when surgery was precluded.

TACE was performed in patients:

(i) who were not suitable for curative treatments because of locally advanced HCC (tumour size >5 cm, or multifocal disease);

(ii) in those for whom percutaneous treatments were precluded due to position (pericholecystic, periportal, subfrenic or subcapsular lesions); and

(iii) in those for whom prior curative treatments had failed.

Table 1 | Demographic, laboratory, clinical and tumour staging characteristics of 84 patients with HCC in compensated cirrhosis treated with TACE

Characteristic	Value
Age – years	68 ± 7
Male – *n* (%)	52 (62)
Aetiology of cirrhosis – *n* (%)	
Anti-HCV positivity	69 (82)
HBsAg positivity	11 (13)
Anti-HCV positivity plus Alcohol abuse	2 (2.5)
NAFLD	2 (2.5)
Performance status* – *n* (%)	
0	68 (81)
1	16 (19)
Hepatic encephalopathy – *n* (%)	
None	84 (100)
Ascites – *n* (%)	
None	84 (100)
Albumin – g/dL	3.6 ± 0.5
International normalised ratio	1.10 ± 0.12
Total bilirubin – mg/dL	1.3 ± 0.7
Child-Pugh Score	5.8 ± 0.9
Classes – *n* (%)	
A	73 (87)
B	11 (13)
Platelet × 10^3/mmc	100 ± 50
Creatinine – mg/dL	0.8 ± 0.3
MELD Score	9.0 ± 1.9
Oesophageal varices – *n* (%)	
None	15 (17.9)
F1	32 (38)
F2	30 (35.7)
F3	7 (8.4)
Portal vein thrombosis – *n* (%)	
None	84 (100)
AFP, median (range) (ng/mL)	20 (3 – 2.000)
Number of nodules (%)	
1	58 (69)
2	15 (18)
3	6 (7)
≥4	5 (6)
Maximum tumour diameter (cm)	3.3 ± 1.6
Number meeting Milan criteria – *n* (%)	
In	60 (71)
Out	24 (29)
BCLC – *n* (%)	
A	44 (52)
B	24 (29)
C	16 (19)
Prior therapy – *n* (%)	
None	61 (73)
Resection	2 (2.3)
Radiofrequency ablation	19 (22.4)
Percutaneous ethanol injection	2 (2.3)

IU, International Units; AFP, alpha fetoprotein; HCV, hepatitis C virus; HBV, hepatitis B virus; BCLC, the Barcelona Clinic Liver Cancer; MELD, Model for End-Stage Liver Disease.

Values are mean ± s.d.

* Eastern Cooperative Oncology Group – performance status.

Exclusion criteria were portal vein thrombosis, impaired liver function (Child-Pugh class ≥B8), widespread cancer (defined as involving more of the 50% of the liver, or with extra hepatic metastasis), hepatic encephalopathy and ascites.

Extra-hepatic disease was assessed with multidetector multiphasic CT and chest radiography. Bone metastases were sought using scintigraphy if clinically suspected.

TACE technique

Each patient underwent standard hepatic angiography using the Seldinger procedure. The catheter tip was advanced as near as possible to the feeding artery. An emulsion of anticancer agent (doxorubicin) and lipiodol, followed by gelatin sponge particles, was carefully injected during the X-ray monitoring. The dose of anticancer agent emulsion and lipiodol, as well as the pieces of embolic materials used for TACE, were based on tumour size and extension of the lesions. TACE was done at baseline and, when there was evidence of any tumour persistence, every 2 months thereafter. It was withheld or discontinued whenever vascular contraindications, poor hepatic function, severe adverse effects or progressive disease developed. One month after every TACE, a multiphasic CT scan was done.

Outcomes and follow-up

The primary outcome was overall survival. Follow-up time was defined as the number of months from first

TACE to orthotopic liver transplantation (OLT), other treatments, last contact with the patient or death.

Response rate magnitude was defined according to the European Association for the Study of the Liver (EASL) criteria.[13] These are addressed by recent guidelines.[14, 15] EASL response criteria are defined as follows:

(i) complete response, defined as absence of any enhancing tissue;

(ii) partial response (PR), defined as >50% decrease in enhancing tissue; and

(iii) stable disease, defined as <50% decrease in enhancing tissue.

Progressive disease is defined as any increase in enhancement of the treated tumour.

As we used an on demand protocol, assessment of response was not done at a fixed time, but after the last performed TACE. The follow-up protocol included clinical assessment by physical examination, ultrasound scan and biochemistry every 3 months and using multiphasic CT scan every 6 months. In our study, TACE-related morbidity was defined as any complication within 2 weeks of each session of TACE. TACE-related mortality was defined as death from a complication within 2 weeks of each session of TACE. Decompensation of liver disease was defined as appearance of ascites, jaundice and/or hepatic encephalopathy during follow-up.

Statistical evaluation. The Kaplan–Meier model was used to estimate survival. Differences in the survival rate were assessed by log-rank testing. Potential prognostic variables were evaluated as predictors of survival both in time-fixed and time-dependent Cox models.[16, 17] In the time-fixed model, only the initial records at the time of first TACE were applied (Table 1). The time-dependent model used the repeated measurements of the potential prognostic variables, with the addition of treatment response, time to progression (TTP) and number of treatments, during follow-up.

All variables studied at univariate analyses were entered into the multivariate analyses. To avoid the effect of co-linearity with performance status, BCLC score was not included in the same multivariate model. Variables with a P value of <0.10 at univariate analysis were included in the final multivariate models. A Cox model was used to identify prognostic factors for mortality in a multiple regression analysis using time-fixed and time-dependent analyses. All P values were two-tailed, and all confidence intervals (CIs) were 95%.

Time-fixed and time-dependent model discrimination were evaluated at 6, 12 and 24 months by the area under incident/dynamic receiver operating characteristic curves (*AUROC*) determined by the Heagerty and Zheng method.[18] At every considered time, *AUROCs* were tested using a Wilcoxon rank sum test with continuity correction.[19, 20]

To have a broader view of the differences between the *AUROCs*, an Integrated Area Under the Curve (*IAUROC*) calculation was made.

All multivariate analyses were done with PROC PHREG in SAS version 8.1 (SAS Institute, Inc., Cary, NC, USA). Model discrimination analyses were carried out with the R Statistical Computing, version 2.10 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient features at baseline

The study population consisted of 84 patients with HCC secondary to cirrhosis of different aetiologies. Of these 84 patients, 61 received TACE as first-line treatment, whereas 23 received it as second-line treatment. The demographical, clinical and tumour staging features of the 84 patients are given in Table 1. A single lesion was observed in 69%, two or three lesions in 25%, and more than three lesions in 6% of patients (Table 1).

At presentation 44 of the 84 patients (52%) were BCLC early (A) stage, 24 were BCLC intermediate (B) stage (29%) and 16 were BCLC advanced (C) stage (19%). Patients at BCLC C stage were classified in this stage because they had symptomatic disease with PS 1.

Follow-up

Three of the 84 patients (4%) were lost at follow-up. During follow-up, 34 patients died (Table 2), 12 patients (14%) were withdrawn for other treatments, whereas 26 (31%) were alive at the end of the study (Table 2). Among the 34 deaths, only three patients (4%) died cancer-free (i.e. without local recurrence, new lesions or distant metastases). Median overall survival after first TACE was 30.5 months [95% confidence interval (CI) 24.0–38.8] for the entire group. The overall survival rates (Figure 1) were 89.6% (95% CI 82.5–97.2); 58.8% (95% CI 46.2–74.9); 35.4% (95% CI 22.3–56.1); 17.2% (95% CI 7.0–41.7); and 5.7% (95% CI 0.9–35.7) at 12, 24, 36, 48 and 60 months, respectively.

Table 2 lists TTP and response rate according to EASL criteria.[11] Response rate after TACE was 76% (complete response, 30%; partial response 34%), and the safety of TACE was found to be acceptable. No patient death was treatment-related. The most common

Table 2 | Follow-up of 84 patients with HCC in compensated cirrhosis treated with TACE

Characteristics	Value
TACE-related mortality – *n* (%)	0 (0)
TACE-related morbidity – *n* (%)	
Abdominal pain	15 (18)
Fever	12 (14)
Vomiting	8 (9)
Acute cholecystitis	1 (1)
Response after TACE – *n* (%)	
Complete response	30 (36)
Partial response	34 (40)
Stable disease	19 (23)
Progressive disease	1 (1)
Patients withdrawn for other treatments – *n* (%)	
OLT	2 (2)
PEI	2 (2)
RFTA	4 (5)
Sorafenib	4 (5)
Time to progression – months (95% CI)	9 (4-18)
Disease-free survival, median – months (95% CI)	10 (9-12)
Death – *n* (%)	34 (40)
Overall survival median – months (95% CI)	30.5 (24.0-38.8)
Decompensation of liver disease – *n* (%)	28 (82)
Portal vein thrombosis – *n* (%)	14 (16.7)

TACE, transarterial chemoembolisation; OLT, orthotopic liver transplantation; PEI, percutaneous ethanol injection; RFTA, radiofrequency thermal ablation; CI, confidence interval.

symptoms were development of transient abdominal pain (18%), fever (14%), and vomiting (9%). The only major complication was acute cholecystitis (1%) (Table 2).

Analysis of factors affecting the survival of patients

Cox regression analysis by time-fixed model showed that performance status (HR 10.9; 95% CI: 4.4–27.1; $P < 0.001$), multiple nodules (HR 3.7; 95% CI: 1.2–8.6; $P = 0.016$) and no prior therapy (HR 3.3; 95% CI: 1.3–10.7; $P = 0.017$) were independent risk factors for mortality (Table 3).

Cox regression analysis by time-dependent model showed that performance status (HR 7.9; 95% CI: 3.63–17.2; $P < 0.001$); no prior therapy (HR 6.3; 95% CI: 1.8–22.67; $P = 0.005$); multiple treatments (HR 0.5; 95% CI: 0.3–0.9; $P = 0.013$); complete response (HR 0.1; 95% CI: 0.03–52; $P = 0.005$); and elevated bilirubin (HR 4.2; 95% CI: 2.2–7.9; $P < 0.001$) were independent risk factors for mortality (Table 3).

When relapsing bilirubin levels as a continuous variable with bilirubin levels as categorical variable (cut-off ≤3 mg/dL) were measured, we obtained similar results. The discriminating ability of time-fixed and time-dependent models in predicting overall survival was evaluated by *AUROC* values at 6 months [0.901 for the time-dependent model, and 0.848 for the time-fixed model

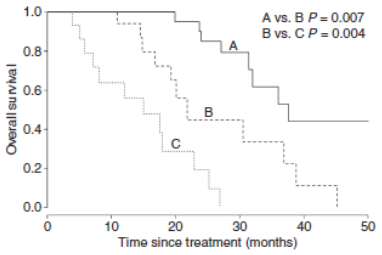

Figure 1 | Probability of overall survival according to Barcelona Clinic Liver Cancer in 84 patients with HCC in compensated cirrhosis treated with TACE.

Table 3 | Multivariate Cox regression models for predicting overall survival in patients with HCC in compensated cirrhosis treated with TACE

Variable (Code)	HR	95% CI	*P*-value
Time-fixed approach			
Performance status* (0/1)	10.9	4.4 – 27.1	<0.001
No prior therapy	3.3	1.3 – 10.7	0.017
Number of nodules (≥3)	3.7	1.2 – 8.6	0.016
Time-dependent approach			
Performance status* (0/1)	7.90	3.63 – 17.23	<0.001
No prior therapy	6.3	1.77 – 22.63	0.005
Number of treatments (Continuous)	0.5	0.31 – 0.87	0.013
Complete response after TACE (yes/no)	0.1	0.03 – 0.52	0.005
Log – bilirubin (Continuous)	4.2	2.18 – 7.89	<0.001

HR, hazard ratio; CI, confidence interval; TACE, transarterial chemoembolisation.

* Eastern Cooperative Oncology Group – performance status.

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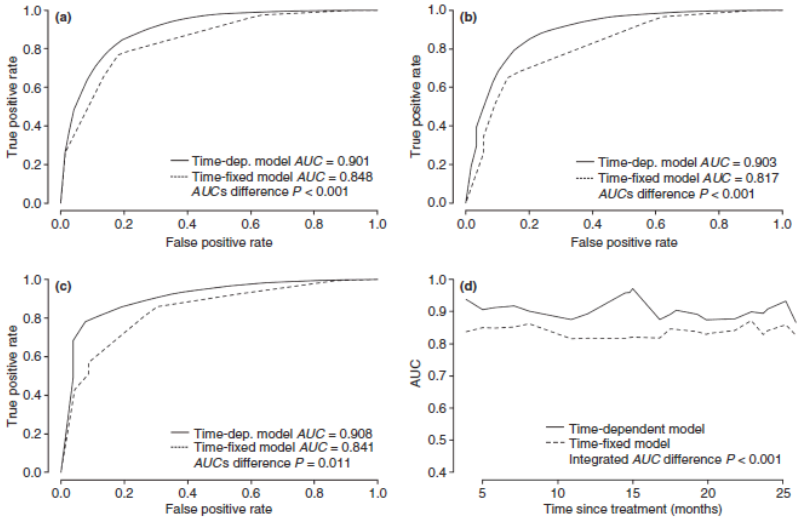

Figure 2 | Receiver Operating Characteristic (ROC) curves and area under the ROC Curve for Time-fixed and Time-dependent Cox regression models At 6 (a), 12 (b) and 24 months (c). (d) Comparison between the Time-dependent and Time-fixed Cox models in terms of integrated *AUROC*s.

(Figure 2a)]; at 12 months [0.903 for the time-dependent model, and 0.817 for the time-fixed model (Figure 2b)]; and at 24 months [0.908 for the time-dependent model, and 841 for the time-fixed model (Figure 2c)]. *AUROC* of the time-dependent model was significantly higher than that of the time-fixed model at all time points [the time-dependent vs. time-fixed models two-sided *P*-values were <0.001, <0.001 and =0.01 at 6, 12 and 24 months, respectively (Figure 2a,b,c)].

The Integrated *AUC* (*IAUC*) of the time-dependent model was significantly higher than that of the time-fixed model (time-dependent model vs. time-fixed model, *P*-value <0.0001), demonstrating a better discriminating capacity of the time-dependent model (Figure 2d).

The estimated probability of survival in the four hypothetical patients treated with TACE who achieved complete response, according to factors significantly predicting mortality by the time-dependent model (i.e. performance status and bilirubin levels) are shown in Figure 3. The 3-year probability of overall survival for a patient with complete response, stable performance

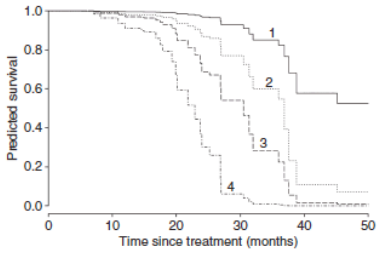

Figure 3 | Estimated probability of overall survival for different patients with HCC treated with TACE, according to variability in predicting factors by Time-dependent Cox regression model. Patients with complete response and (1) Stable performance status and bilirubin levels; (2) Stable performance status and impaired bilirubin levels; (3) Impaired performance status and stable bilirubin levels; (4) Impaired performance status and bilirubin levels.

status 0 and normal bilirubin levels on treatment is 82.5%, and that of a patient with complete response without stable performance status and abnormal bilirubin levels is 0.5%.

DISCUSSION

Hepatocellular carcinoma secondary to cirrhosis is a complex and heterogeneous disease with wide variations during its clinical course.[5, 21] None of the current general prognostic systems has provided confident prediction of survival in individual patients,[10, 12] and so we urgently need specialised models to evaluate patient outcomes within specific allocation treatment groups.[22]

Another important issue is the lack of prognostic tools that are able to adequately express the complexity of the interactions during follow-up between tumour factors and degree of liver failure. As a result, we need models that account for changes during the course of the disease.

In this study, which is to our knowledge the first of its kind, the predictive accuracy of a time-dependent Cox model for overall survival prediction in patients with unresectable HCC and compensated cirrhosis treated with TACE was prospectively compared with that of the most widely-used time-fixed models. The performance of the time-dependent model was significantly better than that of the time-fixed model, and the overall predictive ability of this model, including simple and easy clinical and radiological predictors, was excellent. Moreover, it was uniform over the three time points considered: 6, 12 and 24 months.

This study shows that the key prognostic factors of HCC treated with TACE change over time, and that they can be combined into a specialised model that accurately estimates the risk of mortality at different time points during the post-treatment disease course.

From a practical point of view, the excellent prediction of survival achieved by our model could be useful for:

(i) controlling for confounding factors in observational studies;

(ii) calculating the sample size and stratifying patients in RCTs; and

(iii) assessing treatment effect size in order to formulate therapeutic strategies.

Our study also shows that patients with good performance status may benefit from TACE treatment both in the time-fixed and time-dependent models. The finding that a cancer-related variable, such as the number of tumour lesions assessed at baseline, is an independent predictor for better survival at multivariate analysis is in agreement with the results of a previous study by Takayasu.[23] These two parameters, both included in the BCLC classification, may explain why this staging system provides accurate information on prognosis in the setting of HCC.[24]

An important finding in the present study was the significantly increased risk of death indicated by the time-dependent model in patients with elevating bilirubin levels during follow-up. Therefore, the results of TACE in terms of survival should be carefully evaluated because its indisputable antitumor effects are offset in practice by deterioration in liver function. It is conceivable that a benefit with chemoembolisation could be had only with the sort of careful selection that excludes patients with high risk of progressive liver failure after TACE.[25] That the median survival observed in our study (30 months) was good was likely due to an accurate selection of patients.

As previously reported in the setting of treatment with RFTA,[6] percutaneous ethanol injection (PEI),[26] and, more recently, TACE,[27] it would seem, from the present study, that overall survival depends strictly on complete radiological response. So, complete response is a relevant surrogate end-point that should be planned and carefully assessed by multiphasic CT scan in all patients who undergo TACE.

A general consensus on the optimal schedule of TACE treatment is yet to be reached.[6] In various studies, treatment was repeated at fixed intervals based on a pre-established number of courses, or repeated on-demand based on radiological response. Our study suggests the possibility that repeated courses of treatment are more efficient than single treatment, and that a complete radiological response should be achieved because it is a relevant surrogate end-point. The possibility of achieving this surrogate end point with TACE should be carefully assessed before determining treatment failure after TACE, and then switching to sorafenib.

What are the implications of these results for current practice? In accordance with current AASLD guidelines,[3] we confirmed that mortality risk estimates should be made at baseline with the BCLC staging system. Our study provides further evidence that the evaluation of other simple parameters during the course of treatment, namely performance status, radiological response and bilirubin levels by a time-dependent model can reliably aid in determining whether further sessions of TACE are needed. In the subgroup of patients with the most favourable on-treatment predictors, the probability of 3-year overall survival was 82%.

In patients with complete response, but with coexistence of the most unfavourable on-treatment predictors (worsening of the performance status and increasing of bilirubin levels), the prognosis was very poor. Accordingly, TACE should be repeated until achieving complete necrosis in patients with a good and stable performance status and with relatively preserved liver function (bilirubin level <3 mg/dL).

Our analysis, specifically designed to identify prognostic factors of survival, shows that patients who received TACE as first-line treatment had a higher risk of death than those who received TACE as second-line treatment. The worse survival observed in the first group could be explained by the fact that the first group had a greater number of patients in a more advanced stage than did the second group. Moreover, in our prospective cohort study, 44 of 84 patients (52%) were in BCLC class A, and received TACE. Among these, more-curative treatment failed in 23 patients, who then received TACE as second-line therapy. The remaining 21 could not receive curative treatment because of tumour location and/or comorbidities. It should be recognised that not all patients in real clinical practice defined by each stage of BCLC are ultimately candidates for the suggested treatment modality.

Moreover, the fact that multiple treatments appeared to be a predictor of good outcome may reflect a selection bias due to which patients receiving multiple treatments were those that were healthy enough to tolerate multiple treatments over a long period.

Another weakness of our prognostic model is the lack of data on molecular factors, such as gene expression profiling, which can have some impact on patient's outcome.[28, 29] The predictive ability of our model, including simple and easy clinical and radiological predictors was excellent, underscoring the applicability of our results to new populations and settings, particularly in real clinical practice, where complex and expensive tests are not available.

Finally, we should be particularly concerned about the small number of patients included in this single centre study compared with other prospective, multicenter studies.

Further large-scale prospective studies may prove useful in substantiating the benefit of this new approach.

The available evidence is sufficient to conclude that:

(i) the time-dependent Cox model better predicts overall survival than the time-fixed model;

(ii) patients with a good performance status and with a low number of nodules at baseline, are good candidates for TACE;

(iii) a complete radiological response after TACE significantly increases overall survival, and should therefore be considered a surrogate endpoint of treatment; repeated courses of treatment are more efficient than a single treatment; and

(iv) bilirubin elevation during follow-up significantly increases the risk of death; therefore, treatment should be discontinued when bilirubin exceeds the value of 3 mg%.

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3.2 Targeted Molecular Therapy (Sorafenib)

Until recently, no systemic chemotherapy was shown to be consistently efficacious in treating hepatocellular carcinoma. Sorafenib is a small molecule multikinase inhibitor that is administered orally and has antiproliferative and antiangiogenic properties. In recent randomized, controlled trials, it has been associated with a 37% increase in overall survival (10.7 vs 7.9 months, $p<0.001$), as compared with placebo, in patients with advanced hepatocellular carcinoma and compensated cirrhosis. [11] Rash on the hands and feet, diarrhea, and fatigue are the most commonly reported side effects.

However, since the registration trial was prematurely stopped at the second interim analysis due to significant survival advantage in the active drug arm, benefits and risks of sorafenib therapy could not be adequately assessed, as it occurred in other registration trials evaluating therapeutic regimens. Additional data on safety of sorafenib was also required because registration trials are generally underpowered to evaluate drug tolerability and safety since they rely on rigid protocols and strict exclusion criteria, whereas field practice observational studies, notwithstanding several biases inherent to the traditional cohort studies, offer a chance to properly unravel the clinical effectiveness and toxicity of a drug like sorafenib when administered in real life patients carrying co-morbidities.

Aims

According to all above presented evidences I aimed to further assess, together with my and other Italian groups, risks and benefits of this regimen in clinical practice.

Field-Practice Study of Sorafenib Therapy for Hepatocellular Carcinoma: A Prospective Multicenter Study in Italy

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A multicenter randomized controlled trial established sorafenib as a standard of care for patients with advanced hepatocellular carcinoma (HCC). Because the study was prematurely interrupted due to survival benefits in the sorafenib arm, we conducted an observational study to adequately assess risks and benefits of this regimen in field practice. Starting in 2008, all clinically compensated patients with advanced HCC and those with an intermediate HCC who were unfit or failed to respond to ablative therapies were consecutively evaluated in six liver centers in Italy, for tolerability as well as radiologic and survival response to 800-mg/d sorafenib therapy. Treatment was down-dosed or interrupted according to drug label. Two hundred ninety-six patients (88% Child-Pugh A, 75% Barcelona Clinic Liver Cancer [BCLC]-C, and 25% BCLC-B) received sorafenib for 3.8 months (95% CI 3.3-4.4). Two hundred sixty-nine (91%) patients experienced at least one adverse event (AE), whereas 161 (54%) had to reduce dosing. Treatment was interrupted in 103 (44%) for disease progression, in 95 (40%) for an AE, and in 38 (16%) for liver deterioration. The median survival was 10.5 months in the overall cohort, 8.4 months in BCLC-C versus 20.6 months in BCLC-B patients ($P < 0.0001$), and 21.6 months in the 77 patients treated for >70% of the time with a half dose versus 9.6 months in the 219 patients treated for >70% of the time with a full dose. At month 2 of treatment, the overall radiologic response was 8%. Eastern Cooperative Oncology Group performance status, macrovascular invasion, extrahepatic spread of the tumor, radiologic response at month 2, and sorafenib dosing were independent predictors of shortened survival. *Conclusion*: Overall, safety, effectiveness, and generalizability of sorafenib therapy in HCC was validated in field practice. The effectiveness of half-dosed sorafenib may have implications for tailored therapy. (HEPATOLOGY 2011;54:2055-2063)

Abbreviations: AE, adverse event; AFP, α-fetoprotein; AASLD, American Association for the Study of the Liver Disease; BCLC, Barcelona Clinic for Liver Cancer; CI, confidence interval; CT, computed tomography (contrast-enhanced); ECOG, Eastern Cooperative Oncology Group; FNB, fine-needle biopsy; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HFSR, hand-foot skin reaction; HR, hazard ratio; MRI, magnetic resonance imaging; PS, performance status; RECIST, response evaluation criteria in solid tumors; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

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Hepatocellular carcinoma (HCC) is a lethal condition with an inexorably severe prognosis in the majority of patients who are diagnosed at an advanced, symptomatic stage when the chances for an effective treatment are limited.[1-3] Prognosis is also grim for those patients with an intermediate, less severe tumor disease who are contraindicated for or do not respond to standard-of-care locoablative treatments like transarterial chemoembolization (TACE) or radiofrequency ablation (RFA).[3] In 2008, this scenario was partially subverted by the advent of sorafenib (Nexavar, Bayer Healthcare Pharmaceuticals-Onyx Pharmaceuticals), an oral multikinase inhibitor that, by blocking cell proliferation and angiogenesis of the tumor, resulted in extended survival of patients with an advanced HCC.[4-6] At variance with cytotoxic chemotherapy aimed at tumor cell necrosis, the clinical benefits of sorafenib stem from the ability of the drug to attenuate tumor cell proliferation and progression, occurring at the expense of adverse events (AEs) like diarrhea, fatigue, and skin lesions, whose management, however, was only rarely a challenge for clinicians.[4-7]

A registration trial in the United States and Europe and a confirmatory study in Asia in patients with advanced HCC highlighted a large variability in the clinical activity and tolerability of sorafenib, which was interpreted as a result of large interindividual variability in drug kinetics, in part related to differences in drug bioavailability.[4,8] However, because the registration trial was prematurely stopped at the second interim analysis due to significant survival advantage in the active drug arm (10.7 versus 7.9 months, $P < 0.001$), benefits and risks of sorafenib therapy could not be adequately assessed, as they were in other registration trials evaluating therapeutic regimens.[9] Additional data on the safety of sorafenib are also required because registration trials are generally underpowered to evaluate drug tolerability and safety: they rely on rigid protocols and strict exclusion criteria, whereas field practice observational studies, notwithstanding several biases inherent to the traditional cohort studies, offer a chance to properly unravel the clinical effectiveness and toxicity of a drug like sorafenib when administered in real-life patients who have comorbidities.[10-12] This is not a trivial point, because sorafenib therapy is costly and still in search of optimization due to the lack of serum biomarkers of early response that are deemed necessary to generate response-guided therapeutic algorithms. To bridge the chasm between efficacy and effectiveness of sorafenib therapy, we conducted a field practice observational study in six referral centers in Italy; we recruited patients with advanced HCC as well as patients with an intermediate tumor who failed to respond or had contraindications to locoablative treatments.

Patients and Methods

Study Design. This was a multicenter, investigator driven, observational, noninterventional study to assess the safety and effectiveness of sorafenib in patients with advanced HCC and patients with an intermediate HCC who were not eligible to or failed ablative therapies. The study, which had no industry support, started in July 2008 in six referral centers in Italy with known experience in the treatment of HCC. A kick-off meeting was held to establish common criteria for compliance, type/degree of AE, treatment interruption, and dose reduction. Assignment to sorafenib was not mandated by protocol but reflected the participating physician practice, thereby avoiding additional diagnostic or follow-up interventions. The primary objective was sorafenib safety, and the secondary objectives were treatment effectiveness in terms of overall survival (OS), early radiologic response, and time to radiologic progression. Treatment duration and cumulative dose were additionally evaluated.

Patients. All patients with advanced HCC, i.e., classified as Barcelona Clinic Liver Cancer (BCLC) stage C and those with a BCLC-B stage who were unfit for any or failed to respond to locoablative treatments were consecutively enrolled.[13] Tumors were diagnosed by the criteria of the American Association for the Study of Liver Disease[3] and staged by abdominal dynamic contrast-enhanced computed tomography (CT) or gadolinium-enhanced magnetic resonance imaging (MRI). Each patient underwent also chest radiographic/CT scan and bone scanning as requested by the attending physicians. Exclusion criteria were those of the Italian Drug Regulatory Agency (AIFA),[14] i.e., a performance status (PS) score >2 and clinical decompensation. HCC recurrence after orthotopic liver transplant was also defined as advanced HCC, being therefore indicated for sorafenib therapy. Concomitant anti-

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hepatitis B therapy was allowed. Cirrhosis, which was diagnosed either by histology or clinically, was graded according to the Child-Pugh score as a measure of liver impairment.[15] PS was scored according to the Eastern Cooperative Oncology Group (ECOG).[16]

Written informed consent was obtained from each patient according to the ethics committee and the ethical guidelines of the 1975 Declaration of Helsinki, as updated in 2004.

Routine Chemistries. Blood cell count, serum chemistries, and serum α-fetoprotein (AFP) levels were measured by standard laboratory procedures. Serum hepatitis B surface antigen and antibodies to hepatitis surface antigen, to hepatitis delta virus, to human immunodeficiency virus, and to hepatitis C virus (HCV) were detected by standardized test systems (Ortho DS, Raritan, NJ).

Treatment Schedule, Dose Modification, and Interruption. Sorafenib was administered at a dose of 400 mg twice daily following the indications provided by the manufacturer.[7] Grade 3/4 AEs resulted in dose modification or treatment interruption whenever the AE was clinically relevant. A dose reduction (400 mg once daily) or temporary interruption was maintained until the symptoms resolved to grade 1 or 2 according to the guidelines provided by the manufacturer, followed by a re-escalation to the full dose. The dose was also modified in patients showing grade 2 toxicity on the patient's request or whenever a grade 2 AE was judged clinically relevant. Hepatic deterioration was another criterion for dose modification or interruption. Therapy was discontinued whenever the patient developed unacceptable toxicity, when radiologic or symptomatic progression of HCC occurred, or, by the investigator's judgment, when the patient was unlikely to benefit from further treatment with sorafenib.

Outcome Measures

Safety. In each patient, the medical history, physical examination, blood cell count, serum chemistries, coagulation, and AFP level were obtained at baseline and every 4 weeks thereafter. Each visit included recording of AEs, clinical laboratory tests, physical examination, and assessment of vital signs. Safety was assessed in all patients who received at least one dose of sorafenib; AEs were graded according to the National Cancer Institute's Common Terminology Criteria (version 3.0).[17] Hepatic function deterioration was defined as a Child-Pugh score increase of ≥ 2 points; this was evaluated at each visit and at the predefined time points of weeks 12 and 24 of therapy.

Effectiveness. OS was measured from the date of starting sorafenib therapy until the date of death from any cause or date of last visit. Tumor response was assessed peripherally in each center every 2 months during treatment and at follow-up using CT or MRI, according to modified response evaluation criteria in solid tumors (mRECIST) criteria.[18,19] Each participating center had published expertise in diagnosis and management of HCC, as well as expertise in the application of both RECIST and mRECIST criteria to assess a radiologic response to therapy.[20-25] The time to radiologic progression was defined as the time that elapsed from baseline to disease progression (using mRECIST criteria) according to the radiologic films collected in each center.

Causes of Death. When patients died with radiologic and/or clinical evidence of tumor progression at any time point, these deaths were classified as due to HCC progression. By the same token, when patients died with clinical decompensation such as jaundice, hemorrhage, encephalopathy, or sepsis lacking radiologic signs of cancer progression, these deaths were classified as due to liver failure.

Statistical Analysis. Data were collected by experienced medical personnel involved in the study using a common electronic database. The primary outcomes were assessed by intention-to-treat, while continuous variables were expressed as mean ± standard deviation. Categorical variables were analyzed as frequency and percentages. The following baseline features were considered for univariate analysis: age, gender, ECOG PS, etiology of liver disease, platelet count, albumin level, bilirubin level, alkaline phosphatase, creatinine levels, international normalized ratio, AFP level, esophagogastric varices, macrovascolar invasion, extrahepatic spread, tumor size, number of neoplastic lesions, and treatment center; treatment dose, response, and time to radiologic progression were also considered. Data from patients receiving an anti-HCC treatment other than sorafenib were censored at the time of entry in the second-line regimen. Survival was analyzed by a Kaplan-Meier test, and differences in the survival rates were assessed by the log-rank test.

Variables with a P value < 0.10 at univariate analysis were included in the final multivariate model. Cox's proportional-hazard model was used to identify prognostic factors for mortality in a multiple regression analysis. Multiple logistic regression models were used to assess the relationship of both early radiologic progression and adherence to therapy with the demographic, laboratory, clinical, and tumor staging characteristics of patients. For all analyses, $P \leq 0.05$ was

Table 1. Baseline Demographic, Laboratory, and Clinical Characteristics of 296 HCC Patients Treated With Sorafenib, According to BCLC Tumor Stage

	BCLC-C	BCLC-B	Overall
Patients, no. (%)	222 (75)	74 (25)	296
Age, years*	66 ± 10	69 ± 10	67 ± 10
Male, no. (%)	181 (82)	61 (82)	242 (82)
Etiology, no. (%)			
HCV only	116 (52)	36 (49)	152 (51)
HBV only	43 (19)	15 (20)	58 (20)
Alcohol abuse only	21 (10)	10 (13)	31 (10)
Multiple	22 (10)	6 (8)	28 (10)
Other	20 (9)	7 (10)	27 (9)
ECOG performance status, no. (%)			
0	92 (41)	74 (100)	166 (56)
1	120 (54)	n/a	120 (41)
2	10 (5)	n/a	10 (3)
Child-Pugh class, no. (%)			
A	192 (86)	67 (91)	259 (88)
B	30 (14)	7 (9)	37 (12)
Esophageal varices,† no. (%)			
Absent	76 (41)	35 (49)	111 (43)
Small	87 (47)	30 (42)	116 (46)
Medium/large	22 (12)	6 (9)	28 (11)
Arterial hypertension, no. (%)	91 (41)	29 (39)	120 (41)
AFP ≥ 200 ng/dL, no. (%)	88 (40)	16 (22)	104 (35)
Disease burden, no. (%)			
Macroscopic vascular invasion	115 (52)	n/a	115 (39)
Extrahepatic spread	104 (47)	n/a	104 (35)
One or both	170 (77)	n/a	170 (57)
CLIP score			
0	n/a	n/a	7 (2)
1	n/a	n/a	82 (28)
2	n/a	n/a	102 (34)
3	n/a	n/a	71 (24)
4	n/a	n/a	29 (10)
5	n/a	n/a	5 (2)
Previous therapy	97 (44)	48 (65)	145 (49)

Abbreviations: AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; ECOG, Eastern Cooperative Oncology Group; HCV, hepatitis C virus; HBV, hepatitis B virus; n/a, not applicable.

*Mean ± SD.

†Baseline data on esophageal varices available in 256 patients.

considered statistically significant. All analyses were carried out with SAS version 8.1 software (SAS Institute, Cary, NC).

Results

Patients. By July 2010, 296 patients had been consecutively evaluated (Table 1). There were no relevant differences among the patients enrolled in the six centers with respect to demography, cause or severity of liver disease, previous antitumor therapies, ECOG performance status, and BCLC stage. Chronic HCV infection was the dominant etiology, followed by chronic hepatitis B virus (HBV) infection and alcohol consumption. Two hundred and sixty (88%) patients were in the Child-Pugh A class. None of the 36 Child-Pugh B patients had ascites, clinically overt jaundice, or hepatic encephalopathy. At baseline, 115 patients (39%) had macroscopic vascular invasion by the tumor, whereas 104 (35%) had extrahepatic spread of the tumor, mainly in the abdominal lymph nodes, lungs, and skeleton. Sorafenib was the first treatment modality in 112 (38%) patients, whereas 18 (6%) had HCC recurrence after liver transplantation and 166 (56%) had previously failed locoablative treatment. Two hundred twenty-two (75%) patients were in BCLC-C stage and 74 (25%) in BCLC-B stage, including 26 (35%) who were unfit for locoablative treatment. At the time of analysis (October, 2010), 125 (42%) patients were still alive (55 on treatment) and 171 (58%) had died. Seven (2%) patients who were lost during follow-up were censored at the last visit. The median duration of treatment was 3.8 months (95% CI, 3.3-4.4) including 90 (30%) patients treated for ≥6 months and 41 (14%) treated

Table 2. Treatment-Emergent Adverse Events in the 296 HCC Patients Treated With Sorafenib

Adverse Event*	Any Grade	Grade 1/2	Grade 3/4
Overall, no. (%)	269 (91)	136 (46)	133 (45)
Constitutional symptoms, no. (%)			
Fatigue	195 (66)	121 (41)	74 (25)
Weight loss	115 (39)	97 (33)	18 (6)
Dermatological events, no. (%)			
Hand-foot skin reaction	82 (28)	57 (19)	25 (9)
Rash	15 (5)	8 (3)	7 (2)
Gastrointestinal events, no. (%)			
Diarrhea	103 (35)	85 (29)	18 (6)
Nausea/vomiting	34 (11)	25 (8)	9 (3)
Constipation	18 (6)	18 (6)	0
Stomatitis	17 (6)	17 (6)	0
Bleeding	26 (9)	10 (3)	16 (5)
Arterial hypertension	53 (18)	32 (11)	21 (7)
Any cardiovascular event	15 (5)	8 (3)	7 (2)

*Listed are treatment-emergent adverse events, as defined by the National Cancer Institute Common Terminology Criteria (v3.0), that occurred in at least 5% of patients.

Table 3. Frequency and Causes of Dose Reduction and Permanent Interruption of Treatment

	No. (%)
Dose reduction	161 (54)
AE*	133 (45)
Deteriorated liver function	28 (9)
Permanent discontinuation	233 (79)
AE†	94 (32)
Deteriorated liver function	38 (13)
HCC progression	101 (34)

Abbreviations: AE, adverse event; HCC, hepatocellular carcinoma; HFSR, hand-foot skin reaction.

*Fatigue (n = 63), HFSR (n = 29), diarrhea (n = 23).

†Fatigue (n = 20).

Table 4. Risk Factors Associated With Treatment Interruption due to Intolerance in 296 HCC Patients Treated With Sorafenib*

	Univariate Analysis		Multivariate Analysis	
Predictor (code)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
ECOG performance status (1-2 vs. 0)	1.9 (1.2-2.8)	0.002	1.6 (1.1-2.6)	0.02
Albumin, g/dL (continuous)	0.4 (0.3-0.7)	0.0004	0.6 (0.3-0.9)	0.03
Total bilirubin, mg/dL (continuous)	1.7 (1.2-2.6)	0.003	1.5 (1.01-2.3)	0.03
Age, years (continuous)	1.03 (1.01-1.05)	0.01	1.02 (1.01-1.05)	0.04
Extrahepatic spread (yes vs. no)	0.5 (0.3-0.9)	0.02	–	–

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval.
*To avoid effect of colinearity with variables, BCLC and Child-Pugh scores were not included in the model.

for ≥12 months. The median treatment duration was 4.2 months (95% CI, 3.4-5.0) in the 260 Child-Pugh A patients compared with 2.0 months (95% CI, 0.2-3.8) in the 36 Child-Pugh B patients.

Safety. The overall incidence of AEs was 91% (Table 2). Fatigue, weight loss, diarrhea, hand-foot skin reaction (HFSR), and arterial hypertension were the most frequent AEs, whereas hypothyroidism occurred in 5, perianal fistula in 3, acute pancreatitis in 3, alopecia in 6, and hypophosphatemia in 12 patients. In 133 (45%) patients, AEs were grade 3/4, including fatigue in 74 patients, HFSR in 25, diarrhea in 18, and gastrointestinal bleeding in 16. Myocardial ischemia occurred in three patients. Hepatic function deteriorated in 25 (15%) Child-Pugh A patients and in 2 (8%) Child-Pugh B patients after 12 weeks of therapy and in 17 (16%) Child-Pugh A patients and 6 (40%) Child-Pugh B patients after 24 weeks of therapy. During therapy, 71 (24%) patients developed ascites, 7 (2%) hepatic encephalopathy, and 7 (2%) jaundice.

Dose Reduction and Treatment Interruption. - Treatment was down-dosed in 161 (54%) patients because of AE in 133 (83%) and liver function worsening in 28 (17%) (Table 3). The most frequent AEs leading to dose reductions were fatigue (39%), HFSR (18%), and diarrhea (14%). Treatment was permanently discontinued in 233 (79%) patients, as follows: for AEs in 94 (40%), for severe liver function deterioration in 38 (16%), and for HCC progression in 101 (44%). The main cause of treatment interruption for AE was fatigue, which occurred in 20 (6%) patients within 15 days from baseline.

Ninety-seven (33%) patients discontinued treatment without a previous dose reduction, mainly because of AE (75%), and less frequently (25%) because of liver function deterioration. Duration of treatment was shorter in patients who interrupted for AE than in patients who interrupted for HCC progression (1.7 versus 8.7 months). By multivariate analysis, baseline predictors of premature discontinuation due to intolerance ECOG performance status, serum albumin, bilirubin levels, and age (Table 4).

A total of 77 (26%) patients received a half-dose of sorafenib for ≥70% of the treatment period, which lasted a median of 6.8 months (95% CI 4.2-9.4). Treatment dose was reduced because of AEs in 71 and because of liver function deterioration in 6. Among the remaining patients, 136 maintained a full dose of sorafenib for a median of 3 months (95% CI 2.2-3.8), whereas 83 received a half-dose for <70% of the whole treatment period of 3 months. In the latter patients, the cause of dose reduction was any AE in 73 and liver deterioration in 10.

Radiologic Response. At month 2 of therapy, 2 (1%) patients had a complete response, 22 (7%) had a partial response, 217 (73%) had stable disease, and 55 (18%) had progressive disease. By multivariate analysis, younger age, extrahepatic spread of tumor, and ECOG

Table 5. Risk Factors for Early (Month 2) Radiological Progression during Sorafenib Treatment in 296 HCC Patients*

	Univariate Analysis		Multivariate Analysis	
Predictor (code)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age, years (continuous)	0.95 (0.9-0.97)	0.07	0.95 (0.9-0.98)	0.003
Extrahepatic spread (yes vs. no)	2.7 (1.5-4.9)	0.001	2.2 (1.1-4.2)	0.010
ECOG performance status (1-2 vs. 0)	1.9 (1.1-3.1)	0.01	1.8 (1.0-3.1)	0.034
Previous therapy (yes vs. no)	0.6 (0.3-1.1)	0.003	-	-
Macroscopic vascular invasion (yes vs. no)	2.4 (1.3-4.4)	0.004	-	-

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval.
*To avoid effect of colinearity with variables, BCLC and Child-Pugh scores were not included in the model

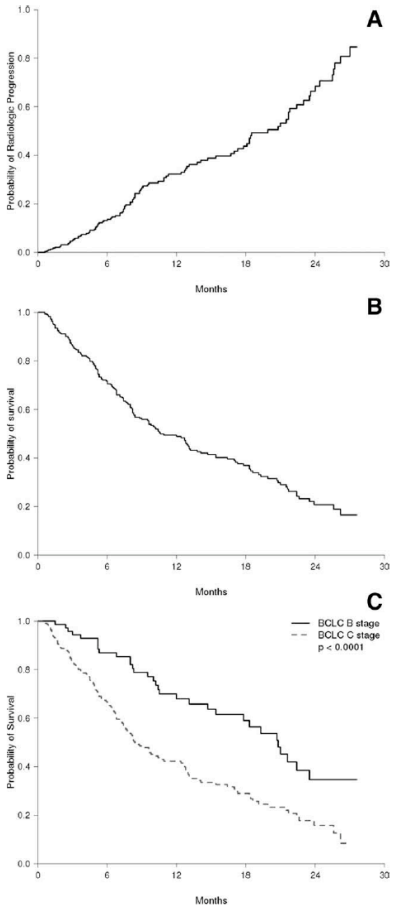

Fig. 1. Kaplan–Meier analysis of 296 patients treated with sorafenib. (A) Time to radiologic progression. (B) Overall survival. (C) Survival according to BCLC.

performance status were associated with an increased likehood of nonresponse (Table 5).

Time to Radiologic Progression. By October 31, 2010, a radiologic progression of the tumor was demonstrated in 101 (34%) patients, with a overall median time to progression of 9.2 (range, 5.5-12.9) months (Fig. 1A). The time to radiologic progression did not differ significantly between BCLC-B and BCLC-C patients (5.5 [range, 2.8-8.5] versus 12 [8-15] months) and between Child-Pugh A and Child-Pugh B patients (10 (range, 5.5-13.5] versus 6.9 [3.5-10] months)

Survival. The median OS was 10.5 months (Fig. 1B), corresponding to 49% of the patients being alive at 1 year. The survival rate of the 74 BCLC-B patients was longer than that of the 222 BCLC-C patients (20.6 versus 8.4 months; $P < 0.0001$; Fig. 1C), as was the median survival of Child-Pugh A compared with Child-Pugh B patients (12.7, 95% CI, 10.6-14.8 versus 7.7, 95% CI, 6.2-9.3). By October 31, 2010, 171 (58%) had patients died of HCC progression (80%), end-stage liver disease (18%), massive gastroesophageal hemorrhage, (1%) or liver-unrelated causes (1%). The distribution of causes of death was the same according to BCLC and Child-Pugh status. Death from decompensation in the first 6 months of therapy occurred more frequently in patients who received a full dose of sorafenib than in half-dosed patients (29 versus 3). By univariate analysis, the variables significantly associated with an increased likehood of mortality were ECOG performance status, macroscopic vascular invasion by the tumor, extrahepatic spread of tumor, age, albumin, total bilirubin, platelet count, and early radiologic progression at month 2. By multivariate analysis, impaired ECOG performance status (hazard ratio [HR] = 1.8, 95% CI 1.4-2.4), macroscopic vascular invasion (HR = 1.7, 95% CI 1.4-2.4), extrahepatic spread (HR = 1.5, 95% CI 1.1-2.4), and early radiologic progression at month 2 (HR = 1.6, 95% CI 1.1-2.4) were the only independent predictors of mortality (Table 6).

The median survival of the 77 patients receiving a half-dose of sorafenib for ≥70% of the treatment period was 21.6 months (95% CI 13.6-29.6) compared with 9.6 months (95% CI 6.9-12.3) for the remaining 219 patients, who maintained full dosing or had a dose reduced for <70% of the treatment period (Fig. 2).

When sorafenib dosing was included in the multivariate analysis of the entire cohort of 296 patients, impaired ECOG performance status (HR = 1.9, 95% CI 1.5-2.5), macroscopic vascular invasion (HR = 1.9, 95% CI 1.4-2.6), extrahepatic spread (HR = 1.4, 95% CI 1.1-1.9), early radiologic progression at month 2 (HR = 1.4, 95% CI 1.1-2.1), and full dose (HR = 1.8, 95% CI 1.4-2.4) were the only independent predictors of mortality. Moreover, multivariate analyses performed excluding patients with early radiologic progression (55 patients) confirmed that full dose was independently correlated with mortality (HR = 1.6, 95% CI 1.04-2.4, $P = 0.031$).

Table 6. Risk Factors for Overall Mortality in 296 HCC Patients Treated With Sorafenib*

	Univariate Analysis		Multivariate Analysis	
Predictor (code)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
ECOG Performance status (1-2 vs. 0)	1.8 (1.4-2.3)	<.0001	1.8 (1.4-2.4)	<0001
Macroscopic vascular invasion (yes vs. no)	2.1 (1.5-2.8)	<.0001	1.7 (1.4-2.4)	0.0009
Extrahepatic spread (yes vs. no)	1.7 (1.2-2.3)	0.001	1.5 (1.1-2.2)	0.01
Lack of radiological response (yes vs. no)	2.6 (1.6-3.6)	<.0001	1.6 (1.1-2.4)	0.02
Age, years (continuous)	0.98 (0.9 - 1)	0.01	–	–
Total bilirubin, mg/dL (continuous)	1.2 (1.1-1.3)	0.03	–	–
Albumin, g/dL (continuous)	0.7 (0.5-0.9)	0.03	–	–
Platelet $\times 10^3$/mmc (continuous)	1.01 (1-1.02)	0.03	–	–

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval.
*To avoid effect of colinearity with variables, BCLC and Child-Pugh scores were not included in the model.

Discussion

This field practice study of 296 consecutively recruited patients in six Italian centers clearly validated sorafenib as a safe and effective treatment modality for advanced HCC. Strengths of this study were the large sample size, which was equal to the treated arm of the registration trial, the consecutive enrollment of real-world patients with broad eligibility criteria reflecting the complexity and diversity of our clinical practice in HCC, and the involvement of centers with well-referenced expertise in diagnosis and treatment of HCC patients, which guaranteed standardized radiologic assessment of the response to sorafenib.[20-25] Another strength of our pragmatic study was the outstanding level of patient retention (98% of the enrolled patients had a final assessment) and the use of mRECIST criteria to assess the response to sorafenib; unlike classical RECIST, mRECIST captured changes in tumor vascularization caused by sorafenib in the absence of significant shrinkage of the tumor.[18,19]

In our pragmatic study, sorafenib appeared to be a safe treatment modality, as in the registration and confirmatory trials and a few other uncontrolled studies in Asia and Europe.[5,6,26-29] Fatigue, diarrhea, and HSFR were the dominant AEs in our patients; in the other studies these factors were distributed differently, fatigue being more frequently reported in our patients than in the registration and confirmatory trials (66% versus 20%-20%). In addition, we noticed a fair rate (18%) of arterial hypertension (occurring either *de novo* or as a worsening preexisting event) that occasionally led to dose reduction or interruption of sorafenib therapy. Although the lack of a control group prevented us from accurately weighing the role of arterial hypertension, the significant difference in the rates of arterial hypertension between sorafenib-treated and placebo-treated patients in both registration and confirmatory trials clearly argues in favor of a causal relationship between the vasoactive drug sorafenib and onset or deterioration of arterial hypertension in treated patients.[30] This was even more so in a Phase III study in Japan and Korea in which patients with advanced HCC treated with sorafenib after TACE had much higher rates of arterial hypertension (33%) than placebo-treated controls (9%).[31]

In contrast to previous reports, in our study high rates (45%) of grade 3/4 AEs accounted for the many instances of reduction or interruption of sorafenib. Not unexpectedly, among the 133 patients who had to reduce sorafenib therapy for AEs, the most frequent causes were fatigue (39%), HSFR (18%), and diarrhea (14%); similar findings were reported in the confirmatory trial, in which 31% of sorafenib-treated patients had to down-dose sorafenib because of AEs.[6] From a clinical point of view, more relevant was the finding of dose reduction and interruption of sorafenib therapy occurring as a consequence of liver function deterioration in 17% and 16% of our patients, respectively, i.e., more frequently than in sorafenib-treated patients

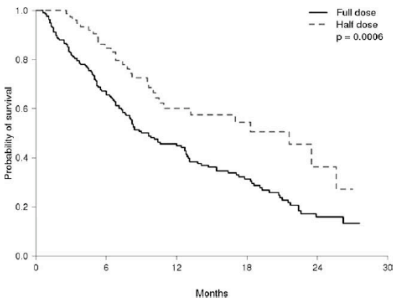

Fig. 2. Kaplan-Meier analysis of overall survival according to the prevalent dose of sorafenib (219 full-dosed or half-dosed <70% treatment period and 77 half-dosed ≥70% treatment period).

in the registration trial (1%) and in the confirmatory trial, in which only 3.5% of the patients had to interrupt treatment due to liver dysfunction and ascites development.[5,6] We think that the higher prevalence of Child-Pugh B patients in our study compared with the registration and confirmatory trials (12% versus 3%-5%) could partially account for the high rates of discontinuation for liver impairment seen in our practice.

Our study differed from Phase III trials in terms of rates of poor tolerability, leading to dose reduction or discontinuation. In fact, only 44% of our patients were able to continue treatment with sorafenib in the absence of tumor progression, whereas a majority of the patients had to interrupt treatment because of the onset of AEs or liver dysfunction, and 26% had to reduce their dosage to a half daily dose (400 mg) of sorafenib for more than 70% of the treatment period, as a consequence of AEs, mainly fatigue. These figures were better in the registration trial, in which 76% of the patients received more than 80% of the planned daily dose of sorafenib.[5]

Our pragmatic study also provided indirect evidence of sorafenib effectiveness, as indicated by the median survival of 10.5 months overlapping with the 10.7 months of survival in treated patients in the registration trial, who had similar ages, rates of ECOG performance status, BCLC stage, and Child-Pugh scores as our patients.[5] The differences in the prevalence of HCV-related tumors between the registration trial and the present study (29% versus 51%) have no clinical consequences, as suggested by the subgroup analysis of the registration trial, which negated any influence of etiology on the response rates to sorafenib in patients with advanced HCC.[32]

As in the registration trial, in our study the survival benefits in sorafenib-treated patients clearly reflected a treatment-related increase of the time to HCC progression. The fact that in our study the time to radiologic progression was significantly longer than in the registration trial (9.2 versus 5.5 months) despite similar duration of treatment (3.8 versus 5.3 months) relates to our choice to apply the more sensitive mRECIST criteria of response assessment, which evaluate changes in arterial vascularity of the tumor occurring in the absence of tumor shrinkage, as previously shown in patients undergoing RFA and TACE.[33]

As in previous studies,[32] sorafenib therapy clearly also benefitted BCLC-B patients who failed to respond or had contraindications to the standard-of-care TACE or other local ablative therapies. A subanalysis of our cohort, in fact, highlighted a clear-cut improvement in survival of BCLC-B patients compared with BCLC-C patients (20.7 versus 8.5 months, $P = 0.0004$), which paralleled the background differences in the spontaneous survival rates between untreated groups of patients reported by Llovet and coworkers (16 versus 6 months).[13]

With all the caveats due to the lack of pretreatment patient stratification for survival predictors, *post hoc* analysis in our study indicated an increase in survival rates for the 77 patients who received a half-dose of sorafenib for more than 70% of the treatment period compared with the 219 patients who were either full-dosed or received a half-dose of sorafenib for less than 70% of the treatment period (21.6 versus 9.6 months). With all the caveats of a *post hoc* analysis, differences in treatment duration between down-dosed patients and full-dosed patients (6.8 versus 3 months) possibly reflect differences in tolerability between regimens, resulting in prolonged exposure to down-dosed sorafenib of less tolerant patients. Increased survival of the latter patients is rather surprising, but it could reflect the ability of a targeted cytostatic molecule like sorafenib to retain anticancer activity at suboptimal dosing, because targeted drugs do not follow the therapeutic paradigm of cytotoxic anticancer drugs, whose clinical activity depends strictly on optimal dosing and achievement of clinically effective levels in patient blood.[34]

It is noteworthy that the rates of liver dysfunction in the registration and confirmatory trials (1% and 3.5%, respectively) were definitely lower than in our pragmatic study, as was the prevalence of Child-Pugh B patients (5% and 3% versus 12%).[5,6] A recent interim report of a large multinational prospective study in patients with advanced HCC further highlights liver impairment as a cause of sorafenib discontinuation, because it demonstrated a direct relationship between the prevalence of AE-related discontinuation and severity of liver impairment assessed by Child-Pugh score.[35]

We also found a correlation of ECOG performance status, liver function, and patient age with an increased likelihood of stopping sorafenib therapy due to poor tolerability; this information might help with clinical counseling and pretreatment patient stratification in the design of therapeutic trials. The original contribution of our study was the identification of independent predictors of radiologic progression of HCC during the first 2 months of therapy, a finding that might help to optimize this costly therapeutic regimen through pretreatment patient stratification. Another original finding of our study was the identification of on-treatment predictors of mortality (such as early radiologic progression and dose regimen) that, if validated by independent studies, could help in identifying a stopping rule and dose tailoring to assist the

clinician in cost-effective management of patients with HCC. Finally, a noteworthy byproduct of the present multicenter pragmatic study was the encouraging evidence of generalizability of sorafenib therapy, as we found no association between treatment center and outcome of therapy.

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CHAPTER 4

DISCUSSION

In the last few decades, the management of HCC has changed significantly, thanks to breakthroughs in the treatment algorithm.

However, spontaneous course of HCC is partially unknown and the choice of treatment is often driven by the cancer stage, the resources available, and the level of practitioner expertise. Curative treatment options for HCC (e.g. liver transplantation, surgical resection, percutaneous ablation) are available if the disease is diagnosed at an early stage.

Despite the use of aggressive local treatments, tumor recurrence and the development of extrahepatic metastases continue to have a significant effect on the overall survival of patients with HCC.

Since only a few randomized, controlled trials have compared the different approaches, most recommendations for staging-guided treatment rely on the findings of observational studies or expert opinion.

Conceivably, the inclusion of molecular variables such as the mutated estrogen receptor, [25] as well as signature gene expression profiling, [26,27] in staging systems could improve their predictive ability.

Even if in absence of molecular data, in our study [28] we found that the survival rate in the placebo or untreated arm of RCTs of HCC patients may be a reliable measure of the spontaneous course of disease and a basic measure for both calculating

sample size and providing a better prognostic stratification in RCTs evaluating new drugs or new multimodal approaches in the palliative setting. Moreover, the 1-year overall survival rate of 34% obtained in our meta-analysis in intermediate/advanced untreated controls can be considered a useful reference value for determining the sample size of future studies and for obtaining indirect comparisons among different trials estimating drug efficacy.

The prognostic value of ascites determines the importance of sub-classifying the intermediate stage in relation to the therapeutic option. In fact, we believe that the benefits of TACE may outweigh the risks for BCLC B patients with Child-Pugh class A or B cirrhosis without ascites, whereas the risks may outweigh the benefits for BCLC B patients with Child-Pugh class A or B cirrhosis with ascites.

About of the treatments of unresectable HCC, as mentioned above TACE is the most widely used first-line treatment for HCCs that cannot be resected.

Despite the many RCTs that have been done to identify the optimal TACE procedure, lack of standardization affects some aspects of treatment, including embolization technique and treatment schedules. [29,30] A relevant clinical question is whether patients should receive repeated courses of TACE at fixed intervals until the planned numbers of courses is reached

or until a complete radiological response is achieved. Moreover, there is no evidence that complete radiological response after TACE is a surrogate end-point strongly linked to overall survival.

Interestingly, in our cohort study, [31] we found that, as previously reported in the setting of treatment with RFTA, [32] PEI, [33] and, more recently, TACE, [34] overall survival depends strictly on complete radiological response. So, complete response is a relevant surrogate end-point that should be planned and carefully assessed by multiphasic CT scan in all patients who undergo TACE. Moreover, we found that patients with a good performance status and with a low number of nodules at baseline, are good candidates for TACE.

A weakness of our prognostic model is the lack of data on molecular factors, such as gene expression profiling, which can have some impact on patient's outcome. Another weakness concerned the small number of patients included in this single centre study compared with other prospective, multicenter studies.

Before the development of sorafenib, first-line systemic therapies for the treatment of unresectable HCC were lacking. Many RCTs had demonstrated that the use of systemic chemotherapy, hormonal compounds, octreotide and interferon in patients with unresectable HCC did not improve survival

compared with no treatment. Such agents are, therefore, discouraged for the treatment of unresectable HCC. [35]

Sorafenib demonstrated an advantage in term of overall survival in two double-blind phase 3 RCTs compared with placebo arm. [11] However, because the registration trial was prematurely stopped at the second interim analysis due to significant survival advantage in the active drug arm benefits and risks of sorafenib therapy could not be adequately assessed and the indiscriminate use of this drug in clinical practice need to be carefully evaluated due to, the lower tolerability profile.

In our large multicenter field practice study, [36] we validated sorafenib as a safe and effective treatment modality for advanced HCC. Strengths of our study were the large sample size, which was equal to the treated arm of the registration trial, the consecutive enrollment of real-world patients with broad eligibility criteria reflecting the complexity and diversity of our clinical practice in HCC, and the involvement of centers with well-referenced expertise in diagnosis and treatment of HCC patients, which guaranteed standardized radiologic assessment of the response to sorafenib.

Interestingly, our study differed from Phase III trials in terms of rates of poor tolerability, leading to dose reduction or discontinuation.

With all the caveats due to the lack of pretreatment patient stratification for survival predictors, *post hoc* analysis in our study indicated an increase in survival rates for the 77 patients who received a half-dose of sorafenib for more than 70% of the treatment period compared with the 219 patients who were either full-dosed or received a half-dose of sorafenib for less than 70% of the treatment period (21.6 versus 9.6 months). Differences in treatment duration between down-dosed patients and full-dosed patients (6.8 versus 3 months) possibly reflect differences in tolerability between regimens, resulting in prolonged exposure to down-dosed sorafenib of less tolerant patients.

In conclusion, HCC is a very heterogeneous disease with a poor prognosis, especially when the disease is diagnosed at an advanced stage. The introduction of targeted therapies, including TKIs, has represented a major advance for the treatment of these patients; however, several issues still remain, and need to be addressed in order to optimize the management of HCC. Given the hyper-vascular nature of HCC it is of interest evaluation of use of sorafenib in combination with other treatments (e.g., TACE).

The combination of loco-regional strategies and sorafenib is currently being explored, as reported in table 2. These combination therapies may be in line, at list in part, with the

increasing mandate for more "personalized" medicine, based upon the peculiar characteristics of each single patients. [37]

Table 2. Ongoing trials on the combination of sorafenib and locoregional strategies for the treatment of HCC.

ClinicalTrials.gov identifier, trial name	Study phase	Agents	Schedule	Sample size (n)	Primary end points	Study completion date (estimated)
NCT00844883	II	DEB TACE + sorafenib	DEB TACE up to four-times/year; sorafenib pre- and post-TACE, then continue as long as beneficial	50	Safety, efficacy	February 2013
NCT00990860, START	II	TACE + sorafenib	TACE + sorafenib	36	Safety, TTP, OS, PFS, number of TACE cycles	Completed
NCT00618384, SOCRATES	II	TACE + sorafenib	Sorafenib 400 mg b.i.d. from time of TACE until PD	72	TTP, safety	Completed
NCT00855218, SPACE	II	DEB TACE + sorafenib vs DEB TACE + placebo	DEB TACE + sorafenib 400 mg b.i.d.	307	TTP, OS, TTUP, time to vascular invasion, time to EHS	December 2011
NCT01004978, ECOG	III	TACE + sorafenib vs TACE + placebo	Sorafenib 400 mg b.i.d., TACE beginning after 2 weeks of sorafenib	400	PFS, OS, safety	September 2012
NCT01324076	III	DEB TACE + sorafenib	Sorafenib 400 mg b.i.d., DEB TACE beginning after 3–5 weeks of sorafenib	412	PFS, OS, toxicity, QoL, number of TACE performed, health economics	November 2014
NCT01217034, TACTICS	II	TACE + sorafenib vs TACE + placebo	Sorafenib 400 mg until 2 days before TACE and restarted after 3 days for first TACE 400 mg b.i.d. from second TACE	228	TTUP TTP, OR, OS tumor marker, safety	September 2016
NCT00494299	III	TACE + sorafenib vs TACE + placebo	Sorafenib 400 mg 1–3 months after one or two TACE sessions	458	TTP, OS	Published [36]

Note. Modified from Cabibbo G, et al. Management of cirrhotic patients with hepatocellular carcinoma treated with sorafenib. Expert Rev Anticancer Ther. 2011 Dec;11(12):1807-1816.

Given the complexity of the disease (in particular for the presence of chronic liver disease) and the large number of potentially useful therapies, it is not surprising that the expertise of many physicians is required to provide optimal care to patients with HCC. Patients diagnosed with liver cancer should be referred to multidisciplinary teams including hepatologists, surgical oncologists, transplant surgeons, medical oncologists, radiation oncologists, diagnostic radiologists, and interventional radiologists, all of whom should play an active role in the care of these patients. Treatment decisions should be discussed in multidisciplinary meetings, as no single treatment strategy can be applied to all patients, and treatment must be individualized.

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