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TTP as a surrogate endpoint in advanced hepatocellular carcinoma treated with molecular targeted therapy: meta-analysis of randomised controlled trials

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Background: Time to progression (TTP) is suggested as a reliable endpoint compared with the progression-free survival in the clinical trials of hepatocellular carcinoma (HCC). However, the correlation between TTP and overall survival (OS) has never been studied.

Methods: We searched PubMed and Embase data to obtain data source. Eligible studies were randomised controlled phase III trials, which evaluated the efficacy of systemic chemotherapy or molecular targeted therapy in advanced HCC. The association of treatment effects as shown by the hazard ratio (HR) of TTP and OS in each trial was assessed by the Spearman rank correlation coefficient (r_s) and linear regression analysis. The association between median TTP and OS was also investigated.

Results: Nine studies with a total of 18 treatment arms and 6318 patients were included. Incremental benefit from the study treatment in TTP from each trial was correlated with incremental benefit in OS. The r_s value and R^2 value between log (HR_{TTP}) and log (HR_{OS}) was 0.73 (95% confidence interval (CI) 0.12–0.94, $P=0.024$) and 0.57. The minimum TTP effect to predict a treatment effect on OS was 0.63. Median TTP was associated with median OS. The r_s value between TTP and OS was 0.73 (95% CI 0.40–0.89, $P<0.001$) and the corresponding R^2 was 0.42.

Conclusions: Our study results suggest that TTP could be used as a surrogate marker for OS in the clinical trials of advanced HCC. However, the results suggest modest correlation between treatment effects on TTP and OS.

In 2012, an estimated 782 500 new cases and 745 000 deaths by liver cancer occurred worldwide (Torre *et al*, 2015). The incidence of liver cancer among all cancer is fifth and ninth in men and women, respectively (Torre *et al*, 2015). Most primary liver cancers occurring worldwide are hepatocellular carcinoma (HCC) (Torre *et al*, 2015). Compared with the low incidence of liver cancer, mortality of liver cancer is relatively high. Liver cancer is the second leading cause of cancer death in men and sixth common cause of cancer death in women (Torre *et al*, 2015). The prognosis of HCC is poor as considerable numbers of patients with HCC is diagnosed at advanced stages and have concurrent liver failure (Thomas *et al*, 2010).

HCC is highly refractory to conventional systemic chemotherapy (Zhu, 2006). In advanced disease, molecular targeted agent

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sorafenib has shown efficacy and is the current standard of care (Llovet *et al*, 2008b; Cheng *et al*, 2009). Recently, a number of studies investigated the efficacy of novel molecular targeted agents such as sunitinib, everolimus, brivanib, linifanib, and ramucirumab in advanced HCC (Cheng *et al*, 2013; Johnson *et al*, 2013; Llovet *et al*, 2013; Zhu *et al*, 2014, 2015a, b; Cainap *et al*, 2015). However, all study results turned out to be negative in both first line and second line settings. Recently, regorafenib has shown efficacy in HCC patients who progressed on sorafenib (Bruix *et al*, 2016). At present, sorafenib is the only systemic agent approved for advanced HCC and regorafenib may be an option after failure of sorafenib.

Overall survival (OS) is the most important endpoint in oncology clinical trials. However, OS can be affected by sequential treatments and requires longer follow-up duration compared with the surrogate endpoints. Using surrogate endpoints may facilitate earlier analysis of study data and provide more direct measure of study efficacy, eliminating the impact of sequential treatments. Progression-free survival (PFS) and disease-free survival is suggested as an appropriate surrogate endpoint in phase II or III clinical trial conducted in solid tumour patients. The correlation between surrogate endpoints and OS has been validated in many types of cancer, including breast cancer, colorectal cancer, and lung cancer (Buyse *et al*, 2000b, 2007, 2009; Sargent *et al*, 2005; Petrelli and Barni, 2014; Blumenthal *et al*, 2015; Ozer-Stillman *et al*, 2015). However, there is no study that has evaluated the correlation between surrogate endpoints and OS in advanced HCC.

Many trials are being carried out to better understand the molecular pathogenesis of HCC and to develop novel treatments for HCC. However, the design of clinical trials of HCC is difficult as it is a heterogeneous disease in terms of aetiology. The leading cause of HCC in Asia and Africa is hepatitis B virus (HBV) compared with hepatitis C virus (HCV) in Europe and North America (Bosch *et al*, 1999). Non-viral causes such as alcoholic cirrhosis and many inherited metabolism disease (Wilson's disease, hemochromatosis, etc.) can also develop HCC (Fattovich *et al*, 2004). Heterogeneous population included in the HCC clinical trial can confound the study results. In addition, many patients with HCC have concurrent liver failure (Llovet *et al*, 2008a). As death resulting from liver failure can confound the potential benefits of effective drug, time to progression (TTP) has been suggested as a reliable surrogate endpoints in HCC compared with PFS (Llovet *et al*, 2008a). However, there is no evidence whether TTP is a reliable surrogate marker in HCC.

The primary purpose of this study was to evaluate the relationship between TTP and OS in advanced HCC.

MATERIALS AND METHODS

Literature review, selection criteria and data extraction. Randomised controlled phase III clinical trials of HCC that evaluated the efficacy of systemic chemotherapy or molecular targeted therapy were identified through PubMed and Embase. Two authors (DWL and KHL) independently carried out a comprehensive systemic search. The main keywords used for the search were 'hepatocellular carcinoma', 'advanced or metastatic' and 'randomized controlled trial'. Article published from January 1, 2008 through July 1, 2015 were included. Eligibility criteria for the included studies were: randomised controlled phase III trials, studies involving patients with advanced HCC and studies evaluating the role of systemic chemotherapy or molecular targeted agent, studies with TTP data. When duplicate publications were identified, we included the most recent article. Studies assessing the efficacy of systemic therapies in combination to loco-regional therapies were excluded.

For each included study, two authors (DWL and KHL) abstracted data for study design, study phase, study period, institution, main inclusion and exclusion criteria, treatment regimen, line of treatment, sample size per treatment arm, baseline characteristics of study patients and data on TTP and OS. All data and analyses were based on all randomly assigned patients using the intention-to-treat approach. Survival data (PFS, TTP and OS) were collected in median data for each trial arms. Hazard ratios (HRs) of control to experimental arm for these endpoints were extracted. When available, confidence intervals (CI) were also collected to evaluate the variations in median outcome.

Statistical analysis. The primary objective of this study was to investigate whether TTP could be used as a surrogate marker for OS in advanced HCC patients treated with systemic chemotherapy or molecular targeted therapy. Subgroup analysis was planned to compare the surrogate role of TTP in first line therapy and second line therapy.

The correlation between HR of TTP and HR of OS and the correlation between median TTP and median OS were evaluated using spearman rank correlation coefficient (r_s or rho). Weighted linear regression analysis was also performed to investigate the correlation between these endpoints and to measure the percentage of OS accounted for by TTP (coefficient of determination, R^2). To account for the difference in sample sizes between arms and studies, data were weighted by the number of patients in linear regression analysis.

The correlation between treatment effects on TTP and OS was evaluated based on the log (HR_{TTP}) and log (HR_{OS}). A linear regression line with 95% CI was used to predict the treatment effects on OS from the observed treatment effects on TTP. Two-sided *P*-values of <0.05 were considered statistically significant. Statistical analysis was performed with the software package (SAS, version 9.2; SAS Institute, Cary, NC, USA).

RESULTS

Study characteristics. Following the systematic literature review, a total of 9 trials were identified with 18 treatment arms and a total of 6318 patients (Table 1). All studies were phase III trials and evaluated the efficacy of molecular targeted agent. Six studies were performed in systemic chemotherapy naive patients and three studies were conducted in patients who failed sorafenib treatment (Llovet *et al*, 2013; Zhu *et al*, 2014, 2015a). The median TTP and OS of each treatment arm ranged from 1.4 to 5.5 months and 4.2 to 10.7 months, respectively.

Most patients in the included studies had Eastern Cooperative Oncology Group performance status 0–1, Barcelona Clinic Liver Cancer stage B-C and child-Pugh score A-B (Table 2). However, the aetiology of HCC was heterogeneous that 18–93% had HBV, 4–30% had HCV and 12–27% had alcoholic liver failure.

TTP as a surrogate marker for OS. All nine studies reported TTP and three studies reported PFS. Correlation between TTP and OS was analysed using the Spearman rank correlation coefficient. Median OS was associated with median TTP and the r_s values between TTP and OS were 0.73 (95% CI 0.40–0.89, $P<0.001$). Using linear regression weighted by sample sizes, R^2 value was 0.41 (95% CI 0.06–0.64, $P=0.004$) and the correlation between OS and TTP was 'OS = 5.59 + 0.87 TTP' (Figure 1).

Although TTP can be used as a surrogate marker, their power of predicting OS can be confounded by following treatments. In this analysis, 12 treatment arms from 6 studies was conducted in treatment naïve population and 6 treatment arms in 3 studies evaluated second line treatment. We investigated the association between TTP and OS according to the treatment line. The r_s values between TTP and OS was 0.59 (95% CI 0.02–0.87, $P=0.043$) and

Table 1. Survival results of included studies

References	Treatment arms	*N*	Line	Arms ID	Endpoints	Median TTP	Median OS	HR TTP	HR OS
Llovet *et al* (2008b)	Sorafenib	299	1st	1a	TTP	5.5 (4.1–6.9)	10.7 (9.4–13.3)	0.58	0.69
	Placebo	303		1b	TTP	2.8 (2.7–3.9)	7.9 (6.8–9.1)	(0.45–0.74)	(0.55–0.87)
Cheng *et al* (2009)	Sorafenib	150	1st	2a	TTP	2.8 (2.6–3.6)	6.5 (5.6–7.6)	0.57	0.68
	Placebo	76		2b	TTP	1.4 (1.4–1.6)	4.2 (3.8–5.5)	(0.42–0.79)	(0.50–0.93)
Llovet *et al* (2013)	Brivanib	263	2nd	3a	TTP	4.2	9.4	0.56	0.89
	Placebo	132		3b	TTP	2.7	8.2	(0.42–0.76)	(0.69–1.15)
Johnson *et al* (2013)	Brivanib	577	1st	4a	TTP	4.2 (4.1–4.3)	9.5 (8.3–10.6)	1.01	1.07
	Sorafenib	578		4b	TTP	4.1 (3.1–4.2)	9.9 (8.5–11.5)	(0.88–1.16)	(0.94–1.23)
Cheng *et al* (2013)	Sunitinib	530	1st	5a	TTP	4.1 (3.2–4.1)	7.9 (7.4–9.2)	1.13	1.30
	Sorafenib	544		5b	TTP	3.8 (2.9–4.2)	10.2 (8.9–11.4)	(0.98–1.31)	(1.13–1.50)
	Sunitinib				PFS	3.6 (2.8–4.1)	7.9 (7.4–9.2)	1.13	1.30
	Sorafenib				PFS	3.0 (2.8–4.0)	10.2 (8.9–11.4)	(0.99–1.30)	(1.13–1.50)
Zhu *et al* (2014)	Everolimus	362	2nd	6a	TTP	3.0 (2.8–4.0)	7.6 (6.7–8.7)	0.93	1.05
	Placebo	184		6b	TTP	2.6 (1.5–2.8)	7.3 (6.3–8.7)	(0.75–1.15)	(0.86–1.27)
Cainap *et al* (2015)	Linifanib	514	1st	7a	TTP	5.4 (4.2–5.6)	9.1 (8.1–10.2)	0.76	1.05
	Sorafenib	521		7b	TTP	4.0 (2.8–4.2)	9.8 (8.3–11.0)	(0.64–0.90)	(0.90–1.22)
	Linifanib				PFS	4.2 (4.1–5.4)	9.1 (8.1–10.2)	0.813	1.05
	Sorafenib				PFS	2.9 (2.8–4.0)	9.8 (8.3–11.0)	(0.697–0.948)	(0.90–1.22)
Zhu *et al* (2015b)	Sorafenib + Erlotinib	362	1st	8a	TTP	3.2	9.5	1.14	0.93
	Sorafenib + Placebo	358		8b	TTP	4.0	8.5	(0.94–1.37)	(0.78–1.11)
Zhu *et al* (2015a)	Ramucirumab	283	2nd	9a	TTP	3.5 (2.8–4.5)	9.2 (8.1–10.6)	0.59	0.87
	Placebo	282		9b	TTP	2.6 (1.6–2.8)	7.6 (6.0–9.3)	(0.49–0.72)	(0.72–1.05)
	Ramucirumab				PFS	2.8 (2.7–3.9)	9.2 (8.1–10.6)	0.63	0.87
	Placebo				PFS	2.1 (1.6–2.7)	7.6 (6.0–9.3)	(0.52–0.75)	(0.72–1.05)

Abbreviations: HR = hazard ratio; OS = overall survival; PFS = progression-free survival; TTP = time to progression.

Table 2. Baseline characteristics of included studies

			ECOG PS			BCLC stage				Child-Pugh score			HCC aetiology		
References	Treatment arms	*N*	0	1	2	A	B	C	D	A	B	C	HBV	HCV	Alcoholic
Llovet *et al* (2008b)	Sorafenib	290	54%	38%	8%	0%	18%	82%	0%	95%	5%	0%	19%	29%	26%
	Placebo	303	54%	39%	7%	0%	17%	83%	0%	98%	2%	0%	18%	27%	26%
Cheng *et al* (2009)	Sorafenib	150	25%	69%	5%	N/A	N/A	95%	N/A	97%	3%	0%	71%	11%	N/A
	Placebo	76	28%	67%	5%	N/A	N/A	96%	N/A	97%	3%	0%	78%	4%	N/A
Llovet *et al* (2013)	Brivanib	263	57%	39%	4%	3%	9%	87%	1%	92%	7%	1%	39%	28%	23%
	Placebo	132	61%	35%	4%	1%	14%	85%	0%	91%	9%	0%	34%	27%	27%
Johnson *et al* (2013)	Brivanib	577	64%	36%	0%	6%	17%	77%	0%	92%	8%	0%	44%	20%	18%
	Sorafenib	578	61%	39%	0%	5%	17%	78%	0%	92%	8%	0%	45%	21%	14%
Cheng *et al* (2013)	Sunitinib	530	53%	47%	0%	0%	13%	87%	0%	100%	0%	0%	55%	21%	17%
	Sorafenib	544	53%	47%	0%	0%	16%	84%	0%	100%	0%	0%	53%	22%	15%
Zhu *et al* (2014)	Everolimus	362	59%	36%	5%	0%	14%	86%	0%	98%	2%	0%	25%	26%	18%
	Placebo	184	57%	40%	3%	0%	14%	86%	0%	99%	1%	0%	28%	23%	25%
Cainap *et al* (2015)	Linifanib	514	63%	37%	0%	0%	16%	84%	0%	94%	6%	0%	54%	25%	13%
	Sorafenib	521	66%	34%	0%	0%	20%	80%	0%	95%	5%	0%	53%	25%	12%
Zhu *et al* (2015b)	Sorafenib + Erlotinib	362	61%	39%	0%	0%	17%	83%	0%	100%	0%	0%	34%	30%	N/A
	Sorafenib + Placebo	358	60%	40%	0%	0%	13%	87%	0%	100%	0%	0%	37%	24%	N/A
Zhu *et al* (2015a)	Ramucirumab	283	56%	44%	0%	0%	12%	88%	0%	56%	44%	0%	35%	27%	N/A
	Placebo	282	54%	46%	0%	0%	12%	88%	0%	54%	46%	0%	36%	27%	N/A

Abbreviations: BCLC = Barcelona Clinic Liver Cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; *N* = number; N/A = not available.

0.87 (95% CI 0.19–0.99, $P = 0.022$), respectively, for first line and second line setting. Corresponding R^2 value was 0.28 (95% CI 0–0.58, $P = 0.075$) and 0.80 (95% CI 0.06–0.90, $P = 0.016$), respectively.

HR_{TTP} as a surrogate marker for HR_{OS}. To evaluate whether the reduction in HR of TTP by a specific treatment can predict its reduction in HR of OS, we analysed the association between HR_{TTP} and HR_{OS}. In six studies, which compared the efficacy of drug *vs* placebo, placebo was used as a control arm. In three studies, which compared the efficacy of novel molecular targeted agent with sorafenib, sorafenib was defined as a control arm. The r_s value between Log (HR_{TTP}) and Log (HR_{OS}) was 0.73 (95% CI 0.12–0.94, $P = 0.024$; Figure 2). The corresponding R^2 was 0.57 (95% CI 0.02–0.77, $P = 0.018$) and the regression equation was log (HR_{OS}) = 0.08 + 0.52 log (HR_{TTP}) indicating that the 10% risk reduction in TTP

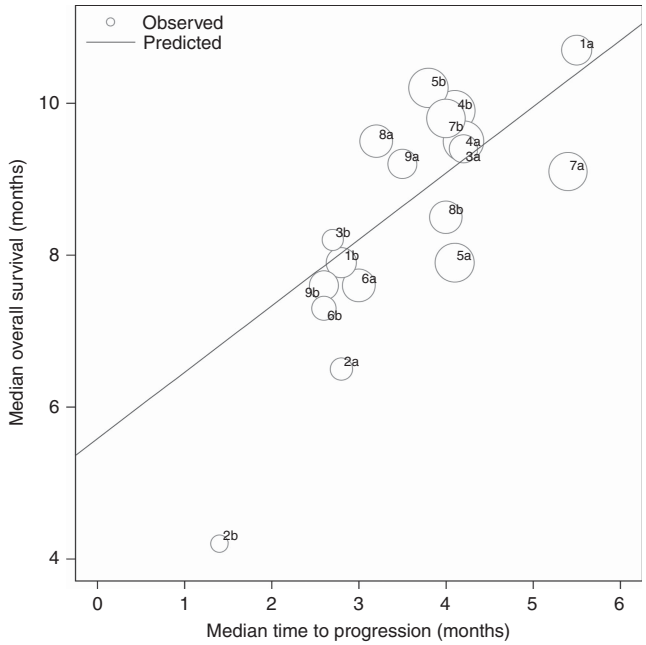

Figure 1. Correlation between median TTP and median OS. Circle size is proportional to the number of randomised patients in each arm. The linear equation was median OS = 5.59 + 0.87 median TTP ($R^2 = 0.42$, $P = 0.004$). Abbreviations: TTP, time to progression; OS, overall survival.

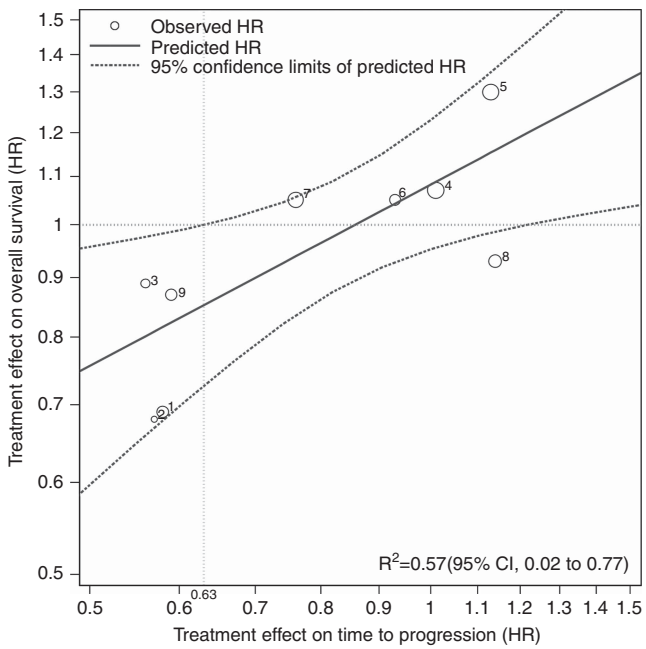

Figure 2. Correlation between treatment effects of TTP and OS. Treatment effects were logarithms of hazard ratios of TTP and OS in each study. Circle size is proportional to the total number of randomised patients in each study. Log scale was used for the *x* axis and *y* axis. The linear equation was log $HR_{OS} = 0.080 + 0.52$ log HR_{TTP} ($R^2 = 0.57$, $P = 0.018$). The vertical line represents the minimum TTP effect to predict a treatment effect on OS. Abbreviations: HR, hazard ratio; OS, overall survival; TTP, time to progression.

would yield 5.2% OS risk reduction as reflected in the slope of 0.52. The minimum TTP effect to predict a treatment effect on OS was 0.63, derived from a vertical line that transects the upper 95% CI and an OS of HR equal to 1.

DISCUSSION

Although OS is the gold standard survival endpoint in the clinical trial, it can be affected by sequential treatment after progression and by crossover from control to experimental arms. In addition, OS requires longer follow-up duration. Using surrogate markers such as TTP and PFS can overcome these problems. PFS is defined as the time from randomisation to documented progression or death from any cause. Although PFS is suggested as a reliable surrogate endpoint in many solid tumours, using PFS as a surrogate marker in HCC might confound treatment outcome as 60–80% of patients with HCC have underling liver cirrhosis and many HCC patients die from the progression of liver failure (Volk and Marrero, 2008). TTP, which death before progression is censored as non-progression, has been suggested as reliable surrogate endpoints in HCC (Llovet *et al*, 2008a). However, the correlation between TTP and OS has never been evaluated. In the present study, we have investigated that TTP could serve as a surrogate marker for OS based on a relationship between HR_{TTP} and HR_{OS} in 9 phase III studies of advanced HCC. In addition, median TTP was associated with median OS.

The correlation of surrogate endpoints and OS can be influenced by sequential treatment after progression. In a subgroup analysis, the r_s value and R^2 value between TTP and OS in the first line studies were 0.59 ($P = 0.043$) and 0.28 ($P = 0.075$). In the second line studies, r_s value and R^2 value between TTP and OS were 0.87 ($P = 0.022$) and 0.80 ($P = 0.016$). The correlation between TTP and OS was higher in the second line setting compared with the first line setting. This could be expected as patients enroled in the first line therapy have a higher chance to receive additional treatment after progression compared with those enroled in the second line therapy. In addition, although there is no effective second line systemic chemotherapy besides regorafenib, which has recently been reported, this result may indicate that the survival of HCC patients treated with molecular targeted agent can be influenced by following local therapy or supportive care. However, we could not perform subgroup analysis using HR due to limited number of study included in the study. Although analysis of median data uses each treatment arm as a variates, paired treatment arm is needed in the analysis of HR. Thus, we cannot confirm that the correlation between TTP and OS is higher in the second line setting compared with the first line setting.

There are several limitations in the present study. A reliable surrogate endpoint should be associated with outcome in both individual-level and trial-level measure (Buyse *et al*, 2000a). This study was a meta-analysis of previous studies and the association of surrogate endpoint and OS was done in trial-level measure but not in individual-level. Analyses of patient-level data are needed to confirm the surrogacy of TTP for OS. Another limitation of the present study is that only nine clinical trials were included in the meta-analysis. Six studies were performed in first line population and only three studies evaluated second line treatment population. However, our meta-analysis included all randomised controlled phase III trials evaluating the role of molecular targeted therapy in advanced HCC, which have been reported since the advent of sorafenib. In addition, this is the first meta-analysis to evaluate the association of TTP and OS in advanced HCC.

In conclusion, TTP could be used as a surrogate marker in advanced HCC patients treated with molecular targeted therapy. However, the results suggest modest correlation between treatment effects on TTP and OS. Along with individual-level analysis, additional work is needed to confirm our findings.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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