Phase II trial of bevacizumab and erlotinib as a second-line therapy for advanced hepatocellular carcinoma

Ahmed Omar Kaseb, Humaid Obaid Al-Shamsi, Jeffrey Morris, Michiko Iwasaki, Lianchun Xiao, Reham Abdel-Wahab, Kanwal Pratap Singh Raghav, Manal Hassan, Hesham M. Hassabo, Robert A. Wolff

Department of Gastrointestinal Medical Oncology, Department of Biostatistics, Department of Diagnostic Radiology The University of Texas MD Anderson Cancer Center, Houston, Texas

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

INTRODUCTION

- Sorafenib is the only approved systemic therapy for advanced HCC, but it is very expensive and has shown only modest activity in randomized phase III trials.
- Patients eventually develop either progressive disease or intolerance to sorafenib, presenting a major challenge that warrants the development of second-line therapies for HCC.
- Early clinical studies of bevacizumab and erlotinib in advanced hepatocellular carcinoma (HCC) have shown promising clinical outcomes.

PURPOSE

- To evaluate the efficacy and tolerability of this combination as second-line therapy for HCC refractory to sorafenib.

METHODS

- Prospective single-arm single institutional phase II study
- we enrolled 44 patients with CTP score A-B, ECOG 0-2, advanced HCC that was not amenable to surgical or regional therapies and progressed on sorafenib or could not tolerate it.
- Patients received 10 mg/kg oral bevacizumab every 14 days and 150 mg oral erlotinib daily for 28-day cycles until progression.
- Tumor response was evaluated every 2 cycles using Response Evaluation Criteria in Solid Tumors.
- The primary endpoint was the 16-week progression-free survival (PFS) rate. Secondary endpoints included time to progression (TTP) and overall survival (OS).

RESULTS

- The 16-week PFS rate was 43% (95% CI: 28-59%)
- At 16 weeks, 4 patients (9%) achieved partial response, 18 patients (41%) had stable disease, 4 patients (9%) had progressive disease, and 3 patients (7%) were not evaluable for response evaluation.

Table 1: Baseline patients' characteristics

Variable	No. (%)
Median age ± SD	63.05 ±11.46
Male	33 (75 %)
Presence of Cirrhosis	19 (43)
Hepatitis C virus	13 (30)
Hepatitis B virus	8 (18)
Alcoholism	10 (23)
Diabetes mellitus	16 (36)
Metabolic syndrome	8 (18)
Follicular nodular hyperplasia	1 (2)
ECOG	
0	15 (34)
1	29 (66)
Ethnicity	
White	26 (59)
Non-white	17 (38)
α-fetoprotein level >400ng/ml	12 (27)
Child-Pugh class	
A	43 (98)
B	1 (2)
>50% liver tumor invlovment	9 (20%)
Multinodularity	34 (77%)
BCLC	
A	2 (5)
B	1 (2)
C	41 (93)
CLIP	
0-2	34 (77)
3	7 (16)
4-6	0
TNM stage	
II	7 (16)
III	8 (18)
IV	29 (66)

- Mean duration of treatment ± SD was 7.53 ± 10.31
- median follow-up time was 33.8 months (95% confidence interval [CI]: 23.5 months-not defined)
- The median TTP was 3.9 months (95% CI: 2.0-8.3 months) and the median OS duration was 9.9 months (95% CI: 8.3-15.5 months).

Table 2: Univariate Cox proportional hazards regression model of associations between overall survival and baseline continuous variables

Covariate	Hazard ratio (95% CI)	*P*
Age at the time of inclusion	0.98 (0.96-1.01)	0.34
Low ALK levels	1.00 (1.000-1.003)	0.04
AFP	1.00 (1.00-1.00)	0.43
Large tumor size	1.12 (1.02-1.23)	0.01
High HB levels	0.69 (0.53-0.89)	0.005

Table3: Univariate Cox proportional hazards regression model of associations between progression-free survival and baseline continuous variables

Covariate	Hazard ratio (95% CI)	*P*
Age at the time of inclusion	0.96 (0.93-0.99)	0.04
Low ALK levels	1.00 (1.000-1.004)	0.02
AFP	1.00 (1.00-1.00)	0.00
Large tumor size	1.06 (0.98-1.16)	0.12
High HB levels	0.73 (0.57-0.95)	0.01

- All patients were assessed for adverse events and classified according to Common Terminology Criteria for Adverse Events (CTCAE)
- The majority of patients developed G1-2 toxcity. And non of them developed G 4 toxcity

Table 4: Adverse events

Adverse event	Toxicity grade, no. (%)		
	1-2	3	4
Fever without neutropenia	1 (2)	0 (0)	0 (0)
Fatigue	23 (51)	6 (13)	0 (0)
Weight loss	10 (22)	0 (0)	0 (0)
Dyspnea	3 (7)	0 (0)	0 (0)
Anorexia	20 (44)	1 (2)	0 (0)
Nausea	16 (36)	1 (2)	0 (0)
Vomiting	13 (29)	0 (0)	0 (0)
Dysphagia	2 (4)	0 (0)	0 (0)
Diarrhea	22 (49)	4 (9)	0 (0)
Constipation	4 (9)	1 (2)	0 (0)
Acne	40 (89)	5 (11)	0 (0)
Gastrointestinal hemorrhage	7 (15)	4 (9)	0 (0)
Other bleeding	13 (29)	0 (0)	0 (0)
Pain	25 (56.8)	2 (4)	0
Anemia	3 (7)	3 (7)	0 (0)
Elevated transaminases	5 (11)	1 (2)	0 (0)
Hand-foot syndrome	3 (7)	1 (2)	0 (0)
Wound infection	1 (2)	0 (0)	0 (0)
Hyperbilirubinemia	13 (29)	1 (2)	0 (0)
Hypokalemia	3 (7)	0 (0)	0 (0)
Dry mouth	2 (4)	0 (0)	0 (0)
Dry eyes	1 (2)	0 (0)	0 (0)
Hypertension	7 (16)	1 (2)	0 (0)
Hyperpigmentation	1 (2)	0 (0)	0 (0)
Hypomagnesemia	7 (16)	0 (0)	0 (0)
Nail changes	4 (9)	0 (0)	0 (0)
Proteinuria	18 (40)	0 (0)	0 (0)
Mucositis	25 (56)	1 (2)	0 (0)
Taste alteration	7 (16)	0 (0)	0 (0)
Voice changes	7 (16)	0 (0)	0 (0)
Thrombus formation	1 (2)	1 (2)	0 (0)

CONCLUSION

- Bevacizumab and erlotinib was tolerable and showed promising activity as a second-line for advanced HCC patients. However, further validation studies are warranted.

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