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Predictors of Apatinib in the Treatment of Advanced Primary Liver Cancer

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Abstract

Objective: The purpose of this study is to investigate the efficacy of Apatinib in the treatment of advanced Primary Liver Cancer (PLC), analyze the factors that influence the efficacy, and find out the biomarkers that effectively predict the efficacy.

Methods: Data from 87 patients with advanced PLC who received Apatinib as first-line treatment at two medical centers were retrospectively analyzed. We analyzed the clinical features and explore the prognostic factors of PLC. We correlated the clinical markers with the efficacy of Apatinib.

Results: The Progression Free Survival (PFS) of the 87 patients was 8.6 ± 1.9 months (95% CI: 5.0 to 12.3). 3-month, 4-month and 5-month disease control rates were 69.0%, 59.2% and 53.5% respectively. Univariate analysis indicated that Alpha-Feto Protein (AFP), Alkaline Phosphatase (ALP), Lactate Dehydrogenase (LDH) and cirrhosis were associated with prognosis ($P<0.05$). Multivariate analysis indicated that ALP was negatively associated with prognosis ($P<0.05$). Chi-square test indicated that the serum AFP and LDH level as well as tumor diameter were statistically different between PFS ≤ 3-month and PFS>3-month groups ($P<0.05$). The survival analysis was conducted that the blood levels of AFP, ALP and LDH as well as with or without cirrhosis before starting Apatinib treatment can influence the survival rate of patients.

Conclusion: Apatinib is an effective treatment for advanced PLC. Serum AFP, ALP and LDH level, as well as whether there is cirrhosis can be used to predict the efficacy of Apatinib.

Keywords: Apatinib; Primary liver cancer; First-line treatment; Efficacy prediction; Prognostic factors

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Introduction

Primary Liver Cancer (PLC) is one of the most common clinical malignant tumors. More than 1.5 million people worldwide are first diagnosed with PLC each year [1,2]. According to data from the Chinese tumor registration in 2015, both the incidence and mortality rates of liver cancer in China ranked No.1 in the world, accounting for about 55% of the cases of liver cancer and 50% of the cases of deaths in the world [3,4]. Surgery is still the first choice of treatment for PLC. Other treatments, such as cutaneous hepatic arterial chemotherapy (TACE), Radio Frequency Ablation (RFA) and traditional Chinese medicine treatments can improve the survival rate of patients and life-improvement therapy can also help to some extent [5,6]. Nevertheless, the long-term outcome of PLC still cannot be improved.

Sorafenib is an effective treatment method for advanced PLC patients [7,8], although its limited efficacy, its high cost and the inability to select effective cohort from large number of patients has limited its clinical usage. With the development of anti-angiogenesis drugs, anti-tumor drugs acting on the signaling pathway of Vascular Endothelial Growth Factor (VEGF) and its receptor have attracted more attention [9-12]. Among them, Apatinib is a new oral anti-angiogenesis small-molecule, which can highly selectively bind and inhibit Vascular Endothelial Cell Growth Factor Receptor-2 (VEGFR-2), thereby inhibiting tumor angiogenesis and tumor growth [13]. It is currently approved for the treatment of advanced gastric cancer [14]. Nonetheless, clinical studies have been carried out to use Apatinib as a treatment for a variety of solid tumors [15-17].

This study analyzes the progress-free survival time, levels of clinical biochemical markers and tumor tissue molecular phenotype in advanced PLC patients who received Apatinib as first-line treatment. We also determined the possible factors which can influence the prognosis. Patients who responded well to the Apatinib treatment were selected from a large number of advanced PLC patients, in an attempt to explore a new and suitable first-line treatment, which can benefit the majority of patients with advanced PLC.

Materials and Methods

Clinical data collection

We collected 87 cases of patients diagnosed with PLC via clinical or pathological diagnosis in the affiliated Union hospital and Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology from February 2015 to December 2017. All patients took Apatinib as the only first-line treatment option. The therapeutic dose for each patient was 250 mg orally daily until intolerance or disease progression. We performed a retrospect review of the cases and analyzed the patients' clinical biochemical characteristics. Eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and normal initial laboratory tests. Those who disagreed and were under 18 years of age have been excluded.

Observation indices

Observed clinical indices include age (≤ 50 y/>50 y), gender, cirrhosis, tumor size (≤ 5 cm/>5 cm); blood biochemical indices: Alpha-Feto Protein AFP (≤ 200 μg/L/>200 μg/L), Cancer Embryo Antigen CEA (≤ 5 μg/L/>5 μg/L), albumin(≤ 35g/L/>35g/L), Alkaline Phosphatase ALP (≤ 140 U/L/>140U/L), Lactate Dehydrogenase LDH (≤ 220 U/L/>22 0U/L), Hemoglobin HB (≤ 120 G/L/>120 G/L), Alamine Aminotransferase ALT (≤ 40 U/L/>40 U/L), Aspartate Aminotransferase AST (≤ 40 U/L/>40 U/L).

Follow-up results

All 87 of patients with PLC were followed up. The average follow-up duration was 12.6 months (range 1 to 33 months). 45 of the 87 cases progressed. CT or MRI images were obtained at least every 3 months during the postoperative follow-up. Tumor recurrence was diagnosed by contrast-enhanced CT or MRI. Information on deaths was obtained from the social security death index, medical records or notifications from family members. The primary endpoint was death or tumor progress.

Statistical treatment

The data were analyzed using SPSS 25.0 statistical software. Chi-square tests were used to compare the age, cirrhosis, albumin, AFP, HB, CEA, ALP, LDH and tumor size between PFS ≤ 3 month and PFS>3 month groups. Kaplan-Meier survival curve was used to analyze the differences in the effects of various clinical biochemical indices on prognosis, univariate prognostic analysis was performed using Log-rank method, and COX regression was performed for multivariate analysis. α=0.05 was the inspection level and $P<0.05$ was considered to be statistical different.

Results

Clinical biochemical data: Among the 87 patients included in this study, 82 were male and 5 were female. The male/female ratio was 16.4:1.0. The average age of onset was 50.4 y (range 27 y to 76 y). 68 cases showed clinical symptoms, among which, 52 cases showed upper abdominal discomfort as the first symptom and 16 cases showed xanthochromia. 19 cases did not show any obvious clinical symptoms and were diagnosed with hepatoncus during physical examination (Figure 1). 76 cases had a history of hepatitis B, and 3 cases had a history of hepatitis C. 48 cases had liver cirrhosis (55.2%). 46 cases (52.9%) had increased levels of serum AFP (>200 μg/L), while 41 cases (37.1%) had levels ≤ 200 μg/L. 21 cases (24.1%) had increased serum ALP levels (>140U/L), while 67 (75.9%) had levels ≤ 140 U/L. 51 cases (58.6%) had increased serum ALT levels (>40 U/L), while 36 (41.4%) had levels ≤ 40 U/L. 50 cases (57.5%) had increased serum AST levels (>40 U/L), while 37 (42.5%) had levels ≤ 40 U/L.24 cases (27.6%) had increased serum LDH levels (>220 U/L), while 17 (19.5%) had levels ≤ 220 U/L and no data for remaining cases. 14 cases (16.1%) had elevated serum levels of CEA (>5 μg/L), and 73 cases (83.9%) had levels ≤ 5 μg/L. All 87 cases received Apatinib as the first-line of treatment. The above information was shown in (Table 1).

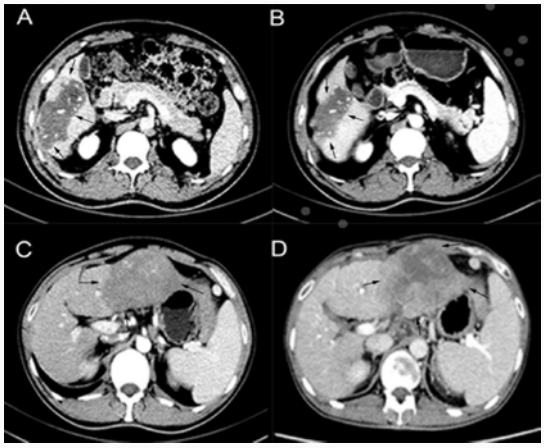

Figure 1: Dynamic liver computed tomography scan revealed the change of liver tumors before (A and C) and after (B and D) treatment. The image B revealed marked reduces of the tumor. The image D revealed slightly enlarged of the tumor and notable necrosis in the center.

Table 1: Main demographic, biochemical, and clinical characteristics of the 87 PLC patients.

Variable	Unit	Value
Age	years	50.4 (27-76)
Gender	male	82 (94.3%)
Albumin	g/L	36 (24-50)
ALT	U/L	71 (2-1478)
AST	U/L	79 (11-1021)
ALP	U/L	63 (16-159)
LDH	U/L	313 (32-2227)
CEA	μg/L	3.7 (1-41)
Tumor size	cm	5.6 (1.5-20)
AFP	μg/L	7071 (2-80000)
HB	g/L	123.6 (70-158)

Data are presented as median (range) or absolute frequency (%).
PLC: Primary Liver Cancer; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ALP: Alkaline Phosphatase; LDH: Lactate Dehydrogenase; CEA: Carcinoembryonic Antigen; AFP: Alpha-Fetoprotein; HB: Hemoglobin

Classification and related prognostic indices: The 87 cases of PLC were divided into 2 groups: Those with PFS ≤ 3 month (47 cases) and those with PFS>3 month group (40 cases). We determined the correlations between age, cirrhosis, albumin, AFP, CEA, HB, LDH, ALP and tumor size with the length of PFS. The results indicated

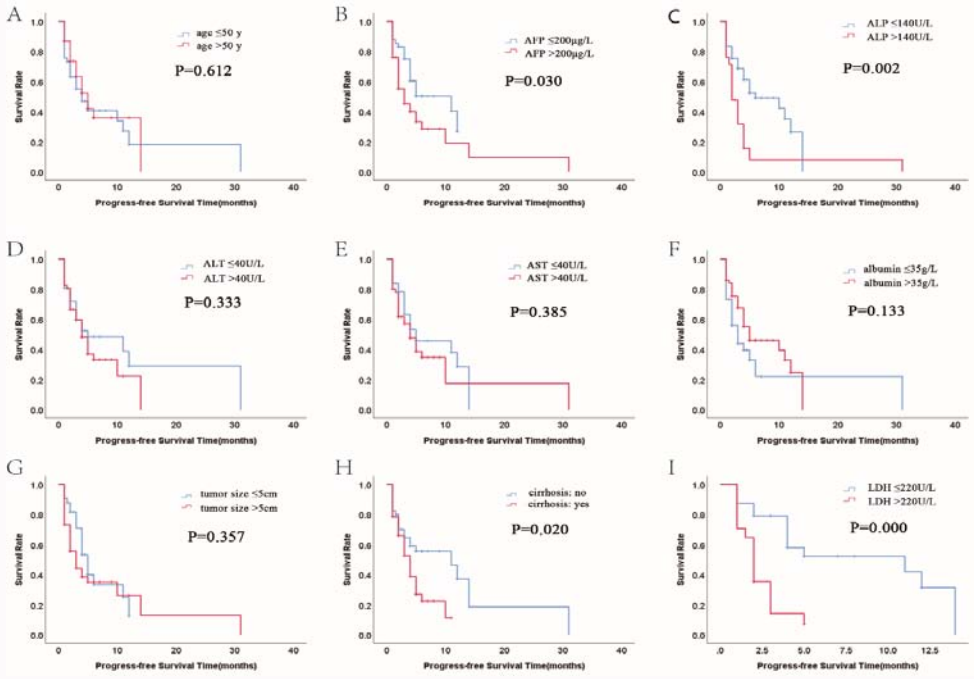

Figure 2: The patients were divided into age ≤ 50 years group and >50 years group (A), ALT ≤ 40 U/L group and >40 U/L group (D), AST ≤ 40 U/L group and >40 U/L group (E), albumin ≤ 35 g/L group and >35 g/L group (F), diameter ≤ 5 cm group and >5 cm group (G), and the survival analysis was conducted respectively, showing no significant difference in progression free survival (P>0.05). At the same time, the patients were divided into AFP ≤ 200 ug/L group and >200 ug/L group (B), ALP ≤ 140 U/L group and >140 U/L group (C), with cirrhosis group and without cirrhosis group (H) and LDH ≤ 220 U/L group and >220 U/L group (I), then the survival analysis was conducted respectively, showing the progression free survival exists significant different (P ≤ 0 05).

Table 2: Correlations of PFS with clinical biochemistry characters (n=87).

	PFS (months)		
Parameters	≤ 3	>3	*P*
Age			0.83
≤ 50y	23	18	
>50y	24	22	
CEA			0.242
≤ 5 μg/L	37	36	
>5 μg/L	10	4	
Tumor size			0.034*
≤ 5 cm	14	19	
>5 cm	28	13	
Unknown	6	7	
AFP			0.022*
≤ 200 μg/L	17	24	
>200 μg/L	30	16	
ALP			0.082
≤ 140 U/L	32	34	
>140 U/L	15	6	
LDH			0.001*
≤ 140 U/L	9	15	
>140 U/L	15	2	
Unknown	22	24	
ALT			0.498
≤ 40 U/L	21	15	
>40 U/L	26	25	
AST			0.66
≤ 40 U/L	21	26	
>40 U/L	16	24	
HB			0.231
≤ 120 g/L	15	9	
>120 g/L	32	31	
Cirrhosis			0.059
Yes	26	16	
no	17	23	
Unknown	2	3	
Albumin			0.114
≤ 35 g/L	20	10	
>35 g/L	27	30	

AFP: Alpha-Fetoprotein; CEA: Carcinoembryonic Antigen; ALP: Alkaline Phosphatase; LDH: Lactate Dehydrogenase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; HB: Hemoglobin
*indicates P<0.05

that AFP, LDH and tumor size were statistical different between the two groups (Table 2). Survival analysis conducted in the 87 cases of patients showed that the PFS was 8.6 ± 1.9 months (95% CI: 5.0 to 12.3). 3-month, 4-month and 5-month disease control rates were 69.0%, 59.2% and 53.5% respectively. The survival analysis was conducted based on groupings on tumor size, AFP levels, albumin levels, ALT levels, AST levels, ALP levels, LDH levels, age and with or without cirrhosis, which were shown in Figure 2. The PFS of patients with AFP (B) levels ≤ 200 μg/L group was higher (7.5 ± 0.8 months)

Table 3: Cox proportional hazard regression analysis of patients' progression free survival.

	Univariable			Multivariable		
Variables	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Age (>50y *vs.* ≤ 50y)	0.875	0.503-1.521	0.636	-	-	-
ALT (>40 U/L *vs.* ≤ 40 U/L)	1.302	0.733-2.314	0.368	-	-	-
AST (>40 U/L *vs.* ≤ 40 U/L)	1.263	0.716-2.229	0.419	-	-	-
HB (>20 g/L *vs.* ≤ 120 g/L)	0.803	0.438-1.472	0.478	-	-	-
ALP(>140 U/L *vs.* ≤ 140 U/L)	2.37	1.315-4.271	0.006*	2.666	1.033-6.877	0.043*
LDH (>5 μ/L *vs.* ≤ 5 μ/L)	3.822	1.654-8.828	0.002*	2.446	0.923-6.478	0.072
Tumor diameter						
(>5 cm *vs.* ≤ 5 cm)	1.289	0.718-2.316	0.395	-	-	-
AFP(>200 ug/L *vs.* ≤ 200 ug/L)	1.785	1.009-3.156	0.046*	1.495	0.632-3.540	0.36
Cirrhosis (yes *vs.* ≤ no)	1.911	1.071-3.408	0.028*	1.204	0.461-3.146	0.704

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; HB: Hemoglobin; ALP: Alkaline Phosphatase; LDH: Lactate Dehydrogenase; CEA: Carcinoembryonic Antigen; AFP: Alpha-Fetoprotein
*indicates p<0.05

than those with AFP levels >200 μg/L group (7.0 ± 1.9 months). The PFS of patients with ALP (C) levels ≤ 140 U/L group was higher (7.7 ± 0.7 months) than those with ALP levels >140 U/L group (4.8 ± 2.0 months) (P<0.05). The PFS of patients with cirrhosis (H) group was higher (4.6 ± 0.6 months) than those without cirrhosis group (11.4 ± 2.9 months) (P<0.05). The PFS of patients with LDH (I) levels ≤ 220 U/L group was higher (8.2 ± 1.2 months) than those with LDH levels >220U/L group (2.3 ± 0.3 months) (P<0.05). Figure 3 shows that neither age (A) (≤ 50 y *vs.* >50 y), blood levels of ALT (D) (≤ 40 U/L *vs.* >40 U/L),blood levels of AST (E) (≤ 40 U/L *vs.* >40 U/L),blood levels of albumin (F) (≤ 35 g/L *vs.* >35 g/L), nor tumor size (G) (≤ 5 cm *vs.* >5 cm) were not correlated with PFS in PLC patients (P>0.05). Table 3 shows the effect of each clinical biochemical index on prognosis. The blood levels of AFP, ALP and LDH as well as with or without cirrhosis before starting Apatinib treatment can influence the survival rate of patients, which provide a great guiding tool for PLC prognosis. Age, albumin level, AST level, ALT level, albumin level, HB level and tumor size have limited prognostic values. The serum levels of AFP, ALP, LDH and with or without cirrhosis can also be used to predict the efficacy of Apatinib.

Discussion

In recent years, significant progress has been made in the treatment of liver cancer, however, the overall prognosis of patients with advanced PLC is still poor [6,18]. If only the best supportive care is provided, the average survival time of patients in Europe and America is 6-9 months and 3-4 months for Asian patients (except Japan) [19]. In our study, all patients took apatinib as the only first-line treatment option. The PFS of the 87 patients was 8.6 ± 1.9 months (95% CI: 5.0 to 12.3), which was significantly better than previously reported data. We analyzed factors that could affect the survival of these patients.

Tumor angiogenesis is one of the key steps of tumor growth and metastasis. Tumor tissues need to rely on oxygen and nutrients provided by new blood vessels to meet the needs of continuous expansion of the tumor cells. Therefore, an intervention to inhibit tumor vascularization can effectively inhibit tumor growth [12]. VEGF and the downstream signal transduction pathway mediated by its receptor, VEGFR, play an important role in the regulation of tumor angiogenesis. The VEGFR family includes Vascular Endothelial Cell Growth Factor Receptor-1 (VEGFR-1), VEGFR-2, VEGFR-3 and VEGFR-co-receptor neuropilin-1 [9,20,21]. Apatinib mesylate is highly selective in binding and inhibiting VEGFR-2, thus inhibiting tumor angiogenesis and tumor growth [13]. However, there are currently no effective predictors for the efficacy of liver cancer targeted therapy drugs including Sorafenib. Using retrospective analysis of the data from advanced liver cancer patients who received Apatinib as a first-line treatment, this study found clinical characteristics or blood biochemical characteristics capable of predicting the efficacy, which can provide guidance for doctors to choose the suitable medication, and avoid invalid treatment and meaningless financial loss [5].

Further analysis showed that whether the patient has cirrhosis, the levels of AFP, ALP and LDH can influence the disease progression, which might have important guiding value for PLC prognosis. The 87 cases of PLC in this study were divided into good efficacy and poor efficacy groups - whether PFS was more than 3 months and correlation analysis showed that tumor size and the level of AFP as well as LDH had statistical differences between these two groups. Survival analysis and group analysis results were slightly different, most likely because we chose 3 months for PFS when grouping. We chose 3 months because the PFS of patients with advanced PLC is 3-4 months [19]. Therefore, we believed that all the results from the above analysis could be used as a reference. Our data indicate that these factors may be related to the efficacy of Apatinib in treating PLC.

In clinical practice, blood test can be used as a simple, cheap and reliable analytical method to detect the level of these indices. At the same time, the clinical characteristics and blood biochemical indices can be analyzed before treatment, thus providing more tools for the clinical drug selection. Finally, we found that gender, age, transaminase level, albumin level and HB level provide limited guidance for prognostic and efficacy judgment in Apatinib-treated patients.

In conclusion, Apatinib has some clinical efficacy for advanced PLC patients and this study had identified some potential efficacy predicting factors. However, this clinical study is still limited, and the efficacy and predictive indices would need a larger size clinical study to be confirmatory. With its widespread clinical usage, the efficacy and safety of Apatinib will be further validated by additional data.

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