Phase 1 trial of apatinib combined with intensity-modulated radiotherapy in unresectable hepatocellular carcinoma

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Research Article

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Abstract

Background

To investigate the maximum tolerated dose (MTD) of apatinib delivered during and after intensity-modulated radiotherapy (IMRT) for unresectable hepatocellular carcinoma (HCC).

Methods

Patients with unresectable HCC who were not eligible for radiofrequency ablation (RFA), transarterial chemoembolization (TACE), or residual/recurrent after the prior local treatment were enrolled. Patients were scheduled to be treated with IMRT at 50–60 Gy/25–30 fractions. Apatinib was administered concurrently with IMRT and continued after IMRT. In this study, we used a 3 + 3 dose-escalation design. Three dose levels of apatinib (250, 500, and 750mg) were designed. Grade 3 or more severe adverse events (AEs) were defined as dose-limiting toxicities (DLTs). The treatment response was calculated using the Modified Response Evaluation Criteria in Solid Tumour.

Results

Nine patients with Barcelona Clinic Liver Cancer stage C were included in this study. One patient withdrew from the apatinib 250mg group and another patient was added. No DLT occurred in the apatinib 250mg group. Five patients were included in the apatinib 500mg group, and 2 cases of DLT (grade 3 leukopenia) were found among them. Dose escalation was terminated and the MTD was determined to be 250mg. Common AEs of grade 1–2 included fatigue, hypertension, dizziness, bone marrow suppression, and hyperbilirubinemia. The median follow-up time for all patients was 16.0 months. Three patients achieved complete response and another three achieved partial response. The objective response rate was 6/9 (66.7%), and the disease control rate was 9/9 (100%). Three patients relapsed out of the radiation field. The median progression-free survival was 17.0 months, and the median overall survival was 16.7 months.

Conclusions

When combined with IMRT, apatinib 250mg daily was recommended for a phase 2 study of unresectable HCC. The antitumor activity of the combination treatment was encouraging. The safety and efficacy of apatinib combined with IMRT for unresectable HCC should be further investigated in future studies.

Background

Liver cancer is the fourth most common cancer and the second leading cause of cancer-related mortality in China [1, 2]. Hepatocellular carcinoma (HCC) is the most common pathological pattern of primary liver

cancer, accounting for 75–85% of cases [3]. Most patients with liver cancer are asymptomatic and typically unresectable when first diagnosed. Advances in radiotherapy techniques, such as three-dimensional conformal radiotherapy, intensity-modulated radiation therapy (IMRT), and stereotactic body radiotherapy, have allowed for enhanced delivery of higher doses to the tumour while sparing normal liver tissue [4–7]. Radiotherapy has become an important choice for the locoregional treatment of HCC. However, intrahepatic metastasis outside the radiation field is usually identified as the first failure [8]. Thus, a treatment strategy that combines radiotherapy with systemic therapy may be recommended.

Apatinib is a small-molecule receptor tyrosine kinase inhibitor that displays potent inhibitory activity against multiple tyrosine kinases such as vascular endothelial growth factor receptor-2 [9]. Apatinib has been demonstrated to exert potential antitumor activity in multiple solid tumours, such as gastric cancer, ovarian cancer, HCC, colorectal cancer, lung cancer, and osteosarcoma [10–14]. In a placebo-controlled, double-blind, phase 3 clinical study, apatinib as second-line therapy in Chinese patients with advanced HCC showed an increased objective response rate (ORR; 10.7% vs. 1.5%), median progression-free survival (mPFS; 4.5 vs. 1.9 months), and median overall survival (mOS; 8.7 vs. 6.8 months) compared to the placebo group [15]. In a randomised phase 2 clinical study, apatinib in combination with transarterial chemoembolization (TACE) showed an excellent PFS benefit compared to TACE alone (mPFS: 12.5 vs. 6.0 months) in the treatment of HCC [16]. Thus, apatinib is an effective systemic therapy for HCC treatment when used alone or in combination with TACE.

Here, we speculated that apatinib combined with radiotherapy may be an effective therapeutic regimen. However, the safety of this HCC treatment has not yet been investigated. Therefore, we undertook this dose-escalating study to determine the safe dose of apatinib when combined with IMRT in the treatment of patients with unresectable HCC.

Patients And Methods

Patients

Eligible patients were aged between 18 and 75 years with an Estern Cooperative Oncology Group performance score of 0–1. HCC was diagnosed based on a biopsy specimen of the tumour, or imaging criteria (CT/MRI LI-RADS v2017) [17]. Patients with HCC were unresectable or relapsed after surgery and not suitable for re-operation. Patients were not suitable for radiofrequency ablation (RFA) or residual/recurrent RFA. Patients were not suitable for TACE or had no substantial necrosis after TACE treatment. Patients were required to have > 700mL of uninvolved liver with Child-Pugh class A. The white blood cell count was $\geq 3.0 \times 10^9$/L, neutrophils count $\geq 1.5 \times 10^9$/L, platelet count $\geq 75 \times 10^9$/L, bilirubin < 1.5 × upper limit of the normal value (ULN), and alanine transaminase and aspartate transaminase < 2.5 × ULN. Patients infected with hepatitis B virus (HBV) must have had HBV DNA levels < 500 IU/mL. The exclusion criteria were as follows: apatinib allergy; previous systemic therapy history; extrahepatic metastasis; pregnant or lactating women, or women of child-bearing age who did not use adequate contraception; untreated or incompletely treated medical conditions, such as uncontrolled hypertension

and diabetes; human immunodeficiency virus positive; bleeding or clotting disorder; stroke or myocardial infarction within 6 months; and gastroduodenal ulcer or upper gastrointestinal bleeding within 3 months.

In this phase 1 study, a traditional 3 + 3 dose escalation design was used. Apatinib and IMRT were performed on day 1, and apatinib treatment continued after IMRT until the tumour progressed or intolerant toxicity was observed. IMRT in combination with three different dose levels of apatinib (250 mg daily, 500 mg daily, and 750 mg daily) were planned for each group. The apatinib dose was escalated if none of the three patients experienced dose-limiting toxicity (DLT) within 16 weeks after IMRT initiation. If one of the three patients developed DLT, another three patients were recruited to the same dose group. When two or more patients out of the six experienced DLTs in a dose level group, the prior dose level was considered as the maximum tolerated dose (MTD). This study was approved by the Peking University Cancer Hospital Ethics Committee (Beijing, China), and all patients provided written informed consent. The study was registered at www.chictr.org.cn (Registration No. ChiCTR1800018309).

Radiotherapy

Simulating computed tomography (CT) and magnetic resonance imaging (MRI) scans were performed with patients in the supine position, along with thermoplastic mask immobilisation. Image registration was performed between simulating CT and MRI to optimise the target and normal structure delineation using the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA, USA). IMRT planning with 6–10 MV X-rays was performed. The prescription dose was 50–60 Gy in 25–30 fractions. The prescribed dose of radiotherapy was based on the upper limit of dose distribution of normal liver tissue and surrounding organs. The dose constraints of organs at risk were as follows: mean dose (D_{mean}) of normal liver volume < 24 Gy, D_{mean} of kidney < 15 Gy, maximum dose (D_{max}) of stomach < 54 Gy, D_{max} of small intestine < 52 Gy, and D_{max} of spinal cord < 45 Gy.

Safety and Response Evaluation

The severity of adverse events (AEs) was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Grade 3 or more severe AEs in the first 16 weeks after IMRT initiation were defined as DLT [18]. Grade 3 hypertension was not defined as DLT if it could be controlled to grade 0–2 by antihypertensive drugs [19]. The cumulative toxicities from extended treatment cycles were also monitored. The treatment response was evaluated using the Modified Response Evaluation Criteria in Solid Tumours (mRECIST) [20]. CT scans of the chest, abdomen, and pelvis as well as MRI of the liver were performed at baseline, 4 weeks after IMRT, and then every 8–12 weeks.

Statistics analysis

Continuous variables were presented as median (range), while categorical variables were presented in terms of number and percentage. The Kaplan-Meier method was used to calculate the time to progression and survival. OS was defined as the time from the start of treatment to death from any cause or to the last follow-up. PFS was defined as the time from the start of treatment to disease progression or

death. Statistical analyses were performed using IBM SPSS Statistics, version 22.0 software (Armonk, NY, USA).

Results

Patients Characteristics

Nine patients with Barcelona Clinic Liver Cancer stage C stage were enrolled between January 2018 and November 2019. Eight patients had portal vein tumour thrombosis, and one patient displayed invasion of the inferior vena cava but without thrombosis. None of the patients had extrahepatic diseases. The 9 patients were men, with a median age of 50 years (range: 46–72 years). The baseline characteristics of the patients are presented in Table 1.

Table 1
Baseline characteristics of patients

Clinical Characteristics		**Number (%)**
Age (y)	Median (range)	50 (46–72)
Gender	Male	9 (100.0)
	Female	0 (0)
Hepatitis virus	HBV infection	9 (100.0)
	HCV infection	0 (0)
Tumour number	Median (range)	1 (1–2)
Tumour size (cm)	Median (range)	5.0 (1.3–13.2)
Tumour thrombosis	PVTT	8 (88.9)
	IVCTT	0 (0)
Previous therapy	Surgery	1 (11.1)
	TACE	7 (77.8)
	RFA	2 (22.2)
	Systemic therapy	0 (0)

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; PVTT, portal vein tumour thrombosis; IVCTT, inferior vena cava tumour thrombosis; TACE, transarterial chemoembolization; RFA, radiofrequency ablation.

Treatment and Dose Escalation

In the apatinib 250mg group, one patient (case 2) withdrew 5 weeks after the start of treatment. The duration of apatinib treatment was 1.0 month, and no DLT was observed. Therefore, another patient was added (case 4) to the apatinib 250mg group. All three patients (cases 1, 3, and 4) completed the planned treatment, and no DLT occurred during the observation period.

The other 3 eligible patients (cases 5–7) were included in the apatinib 500 mg group, among which 1 patient (case 7) developed DLT (grade 3 leukopenia) 3 weeks after receiving treatment. Two additional patients (cases 8 and 9) were enrolled in this group. After 5 weeks of treatment, DLT (grade 3 leukopenia) occurred in case 9, indicating that DLT occurred in 2 out of the 5 patients in this group. Dose escalation was terminated, and the MTD was determined to be 250 mg.

Safety

All the 9 patients were included in the safety analysis, as shown in Table 2. Within the 16 weeks of treatment, the most common AEs were hyperbilirubinemia (4/4) and hypertension (4/4) in the apatinib 250mg group, including 1 case of grade 3 hypertension, which could be controlled to grade 1 with antihypertensive drugs. In the apatinib 500mg group, leukopenia, neutropenia, and hypertension were observed in all 5 cases. Other common AEs included thrombocytopenia (4/5), hyperbilirubinemia (4/5), dizziness (4/5), fatigue (4/5), nausea (4/5), proteinuria (3/5), headache (3/5), and hand-foot syndrome (3/5).

Table 2
Treatment-related toxicities for each dose cohort during the first 16 weeks of treatment

Adverse events	IMRT + apatinib 250mg			IMRT + apatinib 500mg		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Leukopenia	1	2	0	0	3	2
Neutropenia	2	0	0	2	3	0
Anaemia	1	0	0	1	0	0
Thrombocytopenia	0	1	0	0	4	0
ALT increased	2	0	0	2	0	0
AST increased	1	1	0	2	0	0
Hyperbilirubinemia	2	2	0	3	1	0
Hypoalbuminemia	3	0	0	0	1	0
Proteinuria	0	0	0	2	1	0
Headache	0	0	0	2	1	0
Dizziness	1	2	0	3	1	0
Fatigue	3	0	-	3	1	-
Nausea	2	0	0	3	1	0
Diarrhoea	0	0	0	1	0	0
Hand-foot syndrome	0	0	0	2	1	0
Hypertension*	2	1	1	1	1	3

Abbreviations: IMRT, intensity-modulated radiation therapy; ALT, alanine aminotransferase; AST, aspartate aminotransferase

*One case of grade 3 hypertension in the apatinib 250 mg group and 3 cases of grade 3 hypertension in apatinib 500mg group were found, all of which could be controlled to grade 0–1 and were not defined as dose-limiting toxicities in this combination treatment regimen.

The median apatinib administration time was 7.4 (1.0-10.9) months in the 250mg group and 6.6 (1.1–14.2) months in the 500mg group. In the subsequent apatinib treatment of the 500 mg group, two cases of patients were found with severe AEs. 1 case of liver decompensation occurred within 6.6 months. The patients presented with hypoalbuminemia and ascites and died of hepatic encephalopathy. Another patient developed upper gastrointestinal haemorrhage within 5.3 months, but the bleeding was controlled by symptomatic and supportive treatment. No severe AE was found in the subsequent apatinib treatment of the 250 mg group.

Treatment response and survival

In this study, three patients achieved complete response, while three more achieved partial response. The remaining three patients maintained stable diseases status. The ORR was 6/9 (66.7%), and the disease control rate was 9/9 (100%). The median follow-up time for all patients was 16.0 (range: 6.0–28.0) months. Case 1, case 5, and case 8 patients were relapsed out of the radiation field in 10.2 months, 23.2 months, and 5.5 months, respectively. The median PFS was 17.0 months, and the median OS was 16.7 months.

Discussion

In this dose-escalating study of patients with unresectable HCC, two DLT cases (grade 3 leukopenia) were observed in the apatinib 500 mg group. Therefore, in combination with IMRT, apatinib 250mg daily was considered as the recommended dosage in the phase 2 study.

Hypertension was a commonly observed AE in previous studies of apatinib treatment, and the incidence of hypertension was 40% in the treatment of metastatic gastric cancer [14] and 73% in HCC [21]. Considering that hypertension typically occurs early after apatinib treatment and can be well controlled by antihypertensive agents, well-controlled hypertension was not defined as DLT in this study [19]. Four cases in our study were found to have grade 3 hypertension in the first week of treatment with apatinib, and all cases of hypertension were controlled to grade 0 or 1 through single or combined antihypertensive drugs.

In 2017, Lu et al. [16] demonstrated the efficacy and safety of TACE and apatinib for the treatment of HCC. Twenty patients were allocated to the combined treatment group, in which the apatinib dose was 250–500 mg. The common AEs in the combined treatment group included fever, abdominal pain, nausea, diarrhoea, bone marrow suppression, proteinuria, hand-foot syndrome, and hypertension. Severe AEs occurred in three patients, including hand-foot syndrome, diarrhoea, and upper gastrointestinal haemorrhage. In our study of apatinib and IMRT in the treatment of HCC, AEs of grade 1–2 were common, such as fatigue, hypertension, dizziness, bone marrow suppression, and hyperbilirubinemia. Because of the history of hepatitis or cirrhosis, although grade 1–2 toxicities were all reversible, treatment-associated toxicities should be taken seriously. In the subsequent course of apatinib treatment, one case of liver decompensation occurred within 6.6 months, and the patient died of hepatic encephalopathy. Another patient developed upper gastrointestinal haemorrhage within 5.3 months, but the bleeding was controlled by symptomatic treatment. Given the complications of liver cirrhosis, the occurrence of severe AEs and decompensation-related deaths should be considered in HCC treatment. We thought it important in locally advanced HCC to ensure the safety of radiation therapy and to ensure the tolerance in long-term targeted therapy.

The outcome of systemic treatment alone for HCC was unsatisfactory. In the standard first-line treatment, lenvatinib and sorafenib showed similar survival, and the median survival time was 13.6 months and 12.3 months, respectively [22]. According to the mRECIST evaluation criteria, the ORR and mPFS were

respectively 40.6% and 7.3 months in lenvatinib group, and were respectively 12.4% and 3.6 months in sorafenib group. Systemic therapy combined with effective locoregional therapy is a promising approach in locally advanced HCC. In a previous study, apatinib was shown to be effective in combination with TACE, with the best ORR and mPFS of 60% and 12.5 months, respectively [16]. Similarly, in this study, apatinib combined with IMRT for the treatment of locally advanced HCC also showed an encouraging outcome. The best ORR was 67%. The mPFS was 17.0 months, and the mOS was 16.7 months. In a previous study of our team, 63 patients with HCC and macrovascular invasion, underwent IMRT plus TACE combined with or without sorafenib from 2015–2018 [8]. In the failure pattern analysis, intrahepatic metastasis out of the radiation field was the most common failure in the locoregional treatment group, with an incidence of 57.1%. However, in the locoregional treatment plus sorafenib group, intrahepatic metastasis decreased to 28.6%. Thus, locoregional treatment combined with systemic treatment may be an effective treatment option for locally advanced HCC.

In summary, our findings showed that apatinib 250 mg daily may be a safe dosage when combined with IMRT for the treatment of unresectable HCC. The antitumor activity of the combination treatment was encouraging. However, due to the small sample size, the efficacy reported in this phase 1 study should be interpreted with caution. The safety and efficacy of apatinib combined with IMRT for unresectable HCC should be investigated in future studies.

Declarations

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Conflicts of interest All authors have read the journal's policy and declare no conflicts of interest.

Ethics approval and consent to participate This study was approved by the institutional review board and ethics committee of our institute. Informed consent was obtained from each participant.

Availability of data and codes The statistical datasets and codes used and/or analyzed in the current study are available from the corresponding author (wangweihu88@163.com) on reasonable request.

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