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ORIGINAL ARTICLE

Efficacy of apatinib in advanced hepatocellular carcinoma with lung metastasis: a retrospective, multicenter study

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Summary

Purpose: *Lung is the most common extrahepatic metastatic site for patients with advanced hepatocellular carcinoma (HCC) and has a worse prognosis than intrahepatic metastasis. Apatinib is a receptor tyrosine kinase inhibitor that is promising for HCC treatment. We investigated whether apatinib is particularly effective for advanced HCC with lung metastasis.*

Methods: *Sixty-one study patients with advanced HCC treated with apatinib seen at three different institutions between 2015 and 2018 were identified by retrospective review. Forty-one had lung metastasis (13 multi-organ metastasis and 28 lung metastasis only). Twenty had non-lung metastasis. Treatment consisted of oral apatinib 500 mg once daily. Response was assessed by imaging. The primary endpoint was metastasis-specific (m) progression-free survival (mPFS), for which only progression of metastatic lesions was assessed.*

Results: *Median PFS was 3.37 months (range, 0.6-16.1) for all 61 patients. Objective response (OR) was achieved in 7/61 (11.6%) patients. For the 41 patients with lung metastasis, the median mPFS was 5 months (range, 0.9-21.9), with a mOR rate (mORR) of 22.0% (9/41). The mPFS of the 28 patients with only lung metastasis was better (hazard ratio/HR=0.316; 95% confidence interval/CI=0.144-0.696; log-rank p<0.001) than for the 20 with non-lung metastasis; comparison of the mORR showed similar results (21.4 vs. 5%; p=0.019). For the 13 patients with multi-organ metastasis, the mORR of lung lesions was marginally higher than that of other metastatic lesions (23.1 vs. 0%; p=0.096).*

Conclusions: *Apatinib showed promising therapeutic effects on advanced HCC with lung metastasis, highlighting a population that could benefit preferentially from this treatment.*

Key words: *hepatocellular carcinoma, lung metastasis, apatinib, multicenter, efficacy*

Introduction

Hepatocellular carcinoma (HCC) is the most common type of liver cancer, and is the third leading cause of cancer-related deaths worldwide [1]. The treatment of HCC follows well established guidelines [2,3]. Locoregional therapies, such as surgical resection, transplantation, and ablation, are potential curative options for early-stage disease, while for advanced HCC, which comprises 70-80% of cases diagnosed in China, systemic treatment is recommended with the tyrosine kinase inhibitors sorafenib in first-line and regorafenib and nivolumab (conditionally approved in the USA) in second-line settings [4-7]. However, these drugs demonstrated only a moderate survival benefit in an unselected "all-comer" cohort, indicating that there remains a need to develop new drugs for effective management of this disease within a more specified population selected according to clinical characteristics or biomarkers [8].

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The pattern of progression in HCC patients, which proceeds from increase in intrahepatic/extrahepatic tumor size to development of a new intrahepatic lesion (intrahepatic metastasis) to development of a new extrahepatic lesion, is very important in prognostic prediction, and the appearance of a new extrahepatic lesion is an independent predictor of overall survival (OS) [9,10]. The most frequent site of extrahepatic metastasis in HCC patients is the lungs (followed by lymph nodes, bones, and adrenal glands) [11,12], and there are no specific treatment options for this subpopulation other than the recommendations under guidelines for advanced HCC. Meanwhile, studies by Thomas et al [13] and Tian et al [14] show that HCC patients with lung metastasis are prone to develop drug resistance and do not benefit from sorafenib. Thus, a novel systemic therapy option that can extend survival and control advanced HCC with lung metastasis is urgently needed.

Apatinib is an oral small-molecule tyrosine kinase inhibitor that highly and selectively binds to and inhibits vascular endothelial growth factor receptor (VEGFR)-2, which is available in mainland China, and has shown encouraging antitumor activity and tolerable toxicities in several malignancies, including gastric cancer, ovarian cancer, and breast cancer [15-17]. For advanced HCC, apatinib has reached its primary endpoint in a phase II trial [18] and is currently being investigated in a phase III trial with promising results according to the interim analysis.

In this study, we retrospectively observed the patients who failed to or refused sorafenib treatment and aimed to explore the efficacy and safety of apatinib particularly for patients with advanced HCC with lung metastasis.

Methods

Study design and participants

The medical records of patients with advanced HCC who underwent apatinib therapy between November 2015 and May 2018 at three different institutions in China were retrospectively reviewed. Eligible patients were 18 years or older, diagnosed with HCC based on histopathological findings from tumor tissue or from non-invasive assessment according to the American Association for the Study of Liver Diseases criteria for patients with confirmed cirrhosis, and classified as Barcelona Clinic Liver Cancer (BCLC) stage C or stage B with lung and/or other sites of extrahepatic metastasis or new intrahepatic lesions that had radiographically documented disease progression during or after discontinuation of standard therapy and at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines, and had a Child-Pugh A or B liver function score. Patients who had undergone previous or concurrent locoregional treat-

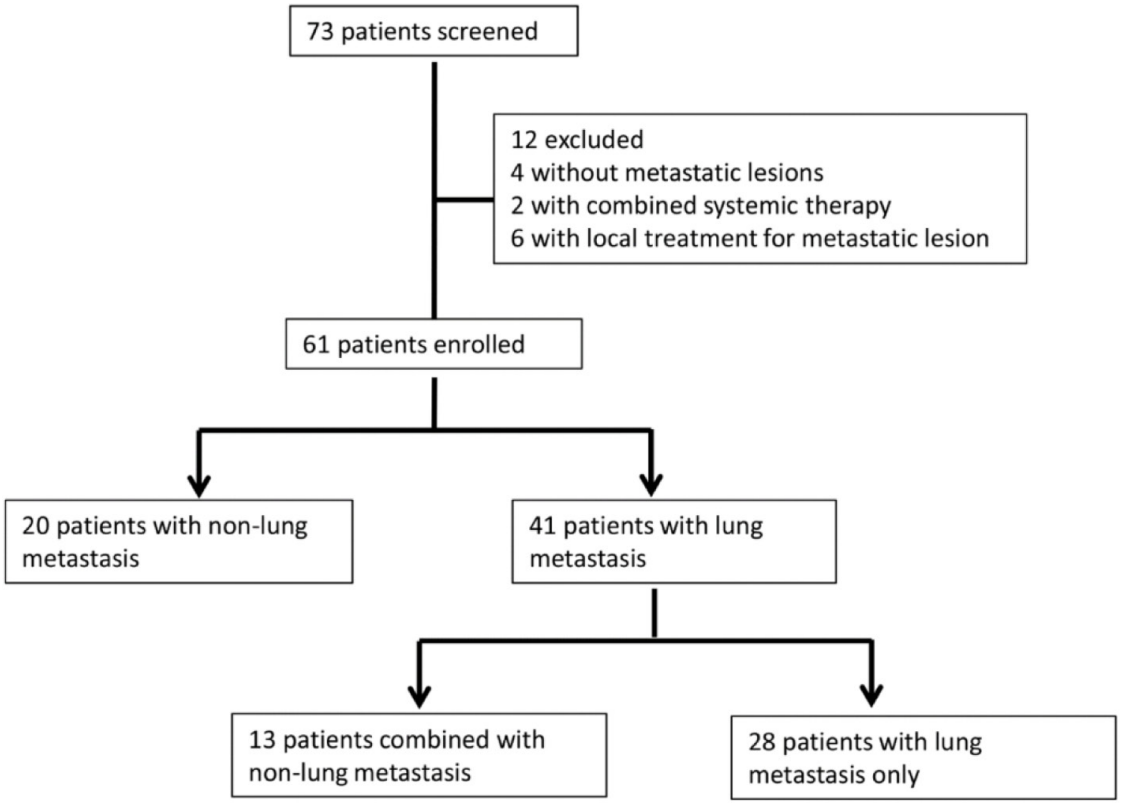

Figure 1. Study chart profile.

ments such as external beam radiotherapy, transarterial chemoembolization, or radiofrequency ablation were only eligible for enrolment if the target was the primary HCC lesion rather than the extrahepatic metastases or new intrahepatic lesions. Other inclusion criteria were an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2, life expectancy of at least 3 months, and adequate hematological and biochemical parameters. Exclusion criteria included systemic drugs concurrently combined with apatinib or administered within 2 weeks before apatinib treatment, locoregional treatments for extrahepatic metastases or the new intrahepatic lesions, known allergies to apatinib or any excipients, uncontrolled blood pressure, coagulation dysfunction with an international normalized ratio >1.7 or platelets $<50\times10^3$, ascites not controlled with diuretics, encephalopathy, active or recent (within 2 weeks) gastrointestinal bleeding, active infection or sepsis, and heart dysfunction. This study was approved by the Ethics Committee of Nanfang Hospital. Signed informed consents were obtained from all participants before the study entry.

Treatment regimens and response assessments

Patients received apatinib orally at an initial dose of 500 mg once daily, continued until disease progression or death, withdrawal of consent from the study, or unacceptable toxic effects. Dose modifications, including dose interruptions and dose reductions, were adopted in cases of grade 3 or 4 adverse events. Either treatment interruptions to alleviate the side effects or dose reductions (to 500 mg on alternate days, or 250 mg once daily or 250 mg on alternate days) could be determined at the clinician's discretion.

Before treating with apatinib, measurable target lesions including primary lesions in the liver and those indicative of emerging disease progression, *i.e.* extrahepatic metastases and new intrahepatic foci (intrahepatic metastasis), were assessed and documented. Tumor response was assessed by investigators according to RECIST 1.1 guidelines, with respect to either only the emerging progression lesions or to the target lesions as a whole, using contrast-enhanced computed tomography and/or dynamic magnetic resonance imaging scans at approximately 8 weeks intervals during treatment. Adverse events were graded and recorded by reviewing the Inpatient Medical Record and follow-up records in each center according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).

Outcomes

The primary endpoint was metastasis-specific progression-free survival (mPFS, for which only the extrahepatic or intrahepatic metastases were assessed), which was defined as the interval from the start of apatinib treatment to metastasis-specific disease progression or death from any cause or, for patients alive without progression, to the last mPFS assessment. Secondary endpoints included progression-free survival (PFS), OS, objective response (OR) rate (ORR), metastasis-specific objective response (mOR) rate (mORR), and safety. PFS was based on the length of time from initial treatment until disease progression or death from any cause or, for patients alive without progression, last PFS assessment. OS referred to the time from administration of apatinib to death from any cause or to the last follow-up. ORR was defined as the proportion of patients who achieved a complete response and a partial response, and mORR was defined similarly with only the metastasis-specific lesions taken into account.

Table 1. Baseline patient characteristics

Age, years	*n (%)*
Median, years (range)	49 (20-72)
<65	58 (95.1)
≥65	3 (4.9)
Gender	
Male	55 (90.1)
Female	6 (9.9)
Smoking	
Ever	17 (27.9)
Never	44 (72.1)
Progression pattern	
Lung metastasis	41 (67.2)
Extrahepatic non-lung metastasis	13 (21.3)
New intrahepatic lesions	20 (31.1)
Portal vein invasion	
Yes	18 (29.5)
No	43 (70.5)
BCLC stage	
B	5 (8.2)
C	56 (91.8)
Child-Pugh score	
A	49 (80.3)
B	12 (19.7)
Treatment setting	
First-line	47 (77.0)
Second-line or more	14 (23.0)
Locoregional therapy in liver	
Yes	37 (60.7)
No	24 (39.3)
HBV-DNA quantitation	
<1000 IU/mL	28 (45.9)
>1000 IU/mL	11 (18.0)
No examination	22 (36.1)
Anti-viral treatment	
Yes	39 (63.9)
No	22 (36.1)
AFP (μg/L)	
≥400	31 (50.8)
<400	24 (39.3)
missing	6 (9.9)

BCLC: Barcelona Clinic Liver Cancer, HBV: hepatitis B virus, AFP: alpha-fetoprotein

Statistics

All statistical analyses were performed using SPSS statistical package version 20.0 (SPSS, Chicago, IL, USA). Kaplan-Meier plots were used to estimate the time to progression and survival time, and the hazard ratio (HR) and 95% confidence interval (CI) were estimated using a non-parametric log-rank test. Response rates in two groups were assessed with the x^2 test or Fisher's exact test. Categorical variables were expressed as numbers and percentages, and continuous variables were expressed as median and interquartile range. $P<0.05$ was considered statistically significant.

Results

Between November 7, 2015, and May 8, 2018, 73 patients with advanced HCC from three medical centers were retrospectively reviewed, and the data collection cutoff date was August 7, 2018. Four patients without assessable metastatic lesions, two who had received concurrently combined systemic therapy and apatinib, and six who had received locoregional treatment for metastatic lesions were excluded, finally leaving 61 study participants. Metastatic lesions included lung, other sites of extrahepatic metastases, and new intrahepatic lesions (intrahepatic metastasis) as defined in the Methods section. As the progression pattern of HCC is very important in prognostic prediction and the development of a new extrahepatic lesion is an independent predictor of OS [9,10], we focused on metastases of the lung, the most common extrahepatic site, as the stratifying factor for further analysis. Of the 61 study patients, 20 had non-lung metastasis and 41 had lung metastasis. And of the 41 patients with lung metastasis, 13 were combined with other sites of extrahepatic metastasis (Figure 1). Baseline patient characteristics are shown in Table 1. The 61 patients (55 male) had a median age of 49 years (range, 20-72); three patients were ≥65 years old. Hepatitis B virus (HBV)-DNA quantitation was available in 39 patients (63.9%), 28 (45.9%) of whom had levels <1000 IU/mL, and 11 (18.0%) of whom had levels >1000 IU/mL for which they received anti-viral treatment. Fifty-six

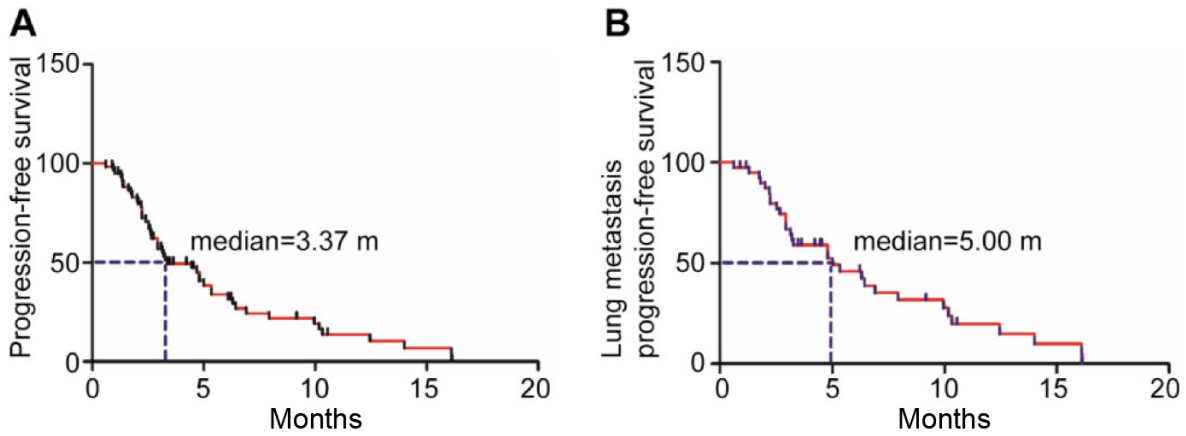

Figure 2. A: Progression-free survival of all patients (n=61). **B:** Lung metastasis progression-free survival (n=41).

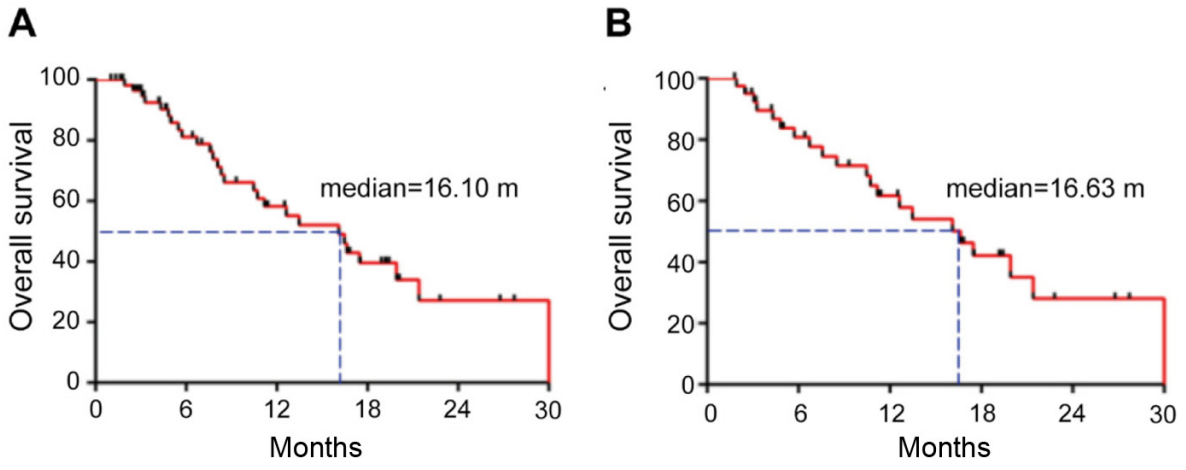

Figure 3. A: Overall survival of all patients (n=61). **B:** Overall survival of patients with lung metastasis (n=41).

patients were diagnosed with BCLC stage C (extrahepatic metastasis or intrahepatic lesions with portal vein invasion), and 6 patients who had new intrahepatic lesions without portal vein invasion were at intermediate stage. Thirty-seven (60.7%) patients received locoregional therapy for the primary target lesions in the liver, and 47 received apatinib in the first-line setting because they either rejected or could not afford treatment with sorafenib.

By the end of the last follow-up, median PFS for all 61 patients was 3.37 months and for the 41 patients with lung metastasis median PFS was 5 months (Figure 2). Median OS for all the patients and for the 41 patients with lung metastasis was 16.10 and 16.63 months, respectively (Figure 3). For the subgroup of 28 patients with lung metastasis only, the median mPFS was significantly improved compared with that of the 20 patients with non-lung metastasis only (6.3 *vs.* 2.5 months, p<0.001; Figure 4A). Median OS in the lung metastasis group (n=41) and non-lung metastasis group (n=20) was 17.5 and 8.3 months, respectively (p=0.346; Figure 4B), and there was an apparent trend toward better OS in patients with lung metastasis, which may show significance with an extended follow-up period.

Seven (11.5%) of the 61 patients had a partial response in whole body evaluation according to RECIST version 1.1 guidelines, and of the 41 patients with lung metastasis, 9 (22%) had a partial response when only lung metastasis was evaluated (Figure 5A). We further assessed the mOR. The mORR was 21.4% (6/28) in patients with lung metastasis only, which was significantly higher than the 5% (1/20) in those with non-lung metastasis

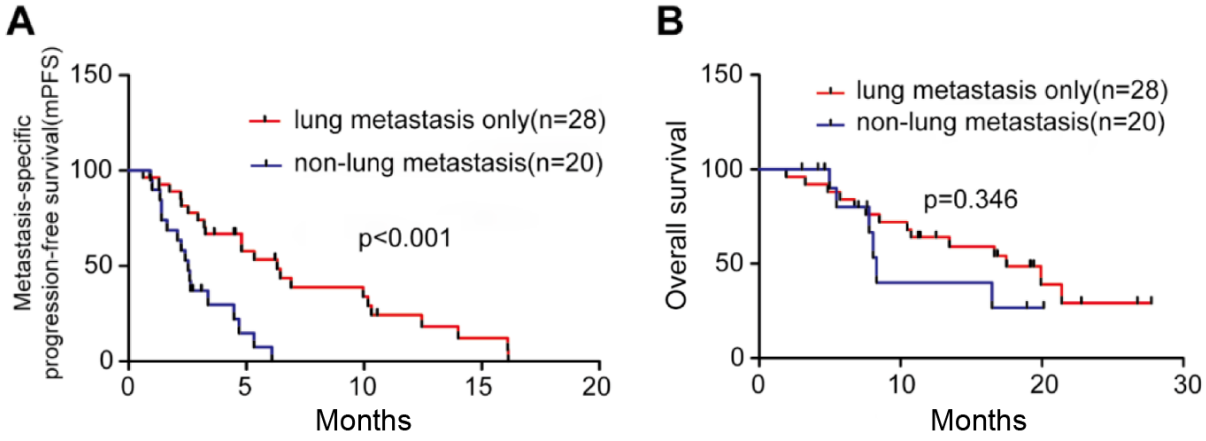

Figure 4. A: Metastasis-specific progression-free survival of patients with lung metastasis only (n=28) and non-lung metastasis only (n=20). **B:** Overall survival of patients with lung metastasis only (n=28) and non-lung metastasis only (n=20).

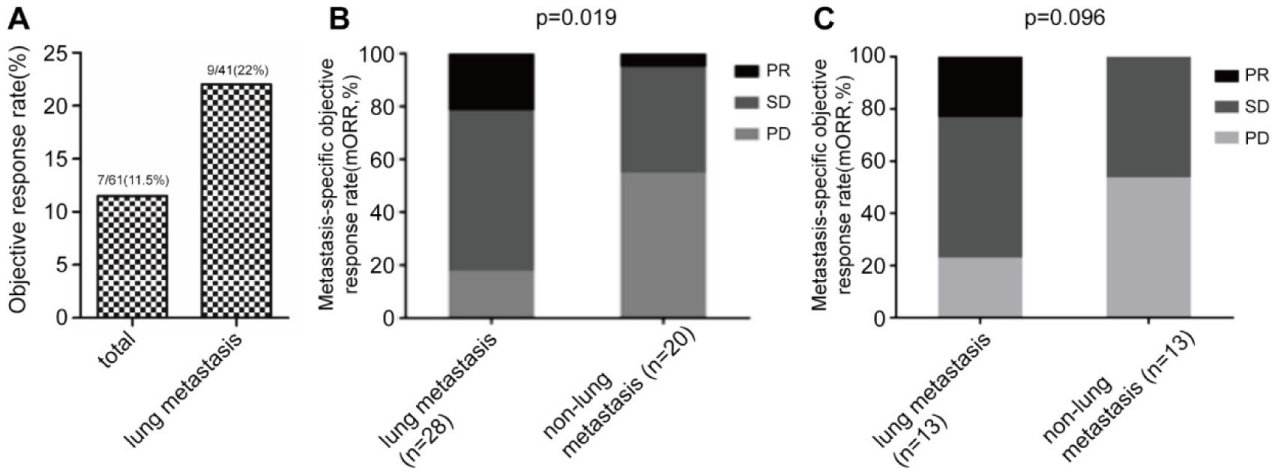

Figure 5. A: Objective response rate evaluating the whole body in 61 patients and lung metastasis only in 41 patients. **B:** Objective response comparing the patients with only lung metastasis (n=28) with those with only non-lung metastasis (n=20). **C:** Objective response of target lesions in patients (n=13) concurrently harboring lung and non-lung metastasis. PR: partial response SD: stable disease, PD: progressive disease

Table 2. Possible apatinib treatment-related adverse events

Adverse events	*Grade 1-2 n (%)*	*Grade 3 n (%)*
Hypertension	9 (14.8)	1 (1.6)
Hand-foot skin reaction	14 (23.0)	3 (4.9)
Diarrhea	7 (11.5)	1 (1.6)
Vomiting	8 (13.1)	0
Fatigue	6 (9.8)	0
Epistaxis	1 (1.6)	0
Headache	3 (4.9)	0
Anorexia	4 (6.5)	0

only (p=0.019; Figure 5B). Among the 13 patients with both lung and non-lung metastasis, only 3 (23.1%) had a partial response for lung metastasis and none had a partial response for non-lung metastasis (p=0.096; Figure 5C).

The total incidence of adverse events (any grade) during Apatinib treatment was 93.4%. Adverse events in the 61 patients mainly consisted of hand-foot skin reaction (27.9%), hypertension (16.4%), diarrhea (13.1%), vomiting (13.1%), and fatigue (9.8%; Table 2). The most common clinically relevant grade 3 events were hand-foot skin reaction (n=3, 4.9%), hypertension (n=1, 1.6%), and diarrhea (n=1, 1.6%). Five patients had dose reductions and 8 interrupted treatment due to adverse events. All toxicities were manageable by treatment interruptions or dose modifications and by providing symptomatic treatment. No grade 4 or 5 adverse events were observed.

Discussion

In patients with metastasis of HCC to the lung, apatinib showed more benefit than in those with non-lung metastasis of HCC, resulting in significantly longer mPFS and OR. It did not afford significant improvement in OS for patients with lung metastasis when compared with those with non-lung metastasis.

Recently, sorafenib and regorafenib have been approved for patients with advanced HCC in first- and second-line settings, respectively, and nivolumab has been conditionally approved for sorafenib-experienced HCC patients in the USA. Three other kinase inhibitors, lenvatinib, cabozantinib, and ramucirumab, have reached their primary endpoint in phase III trials and may be added to the armamentarium of systemic therapies for advanced HCC in the near future. However, there is still a need to develop new drugs for effective management of this disease, especially considering that, other than ramucirumab, which is the first biomarker-guided treatment in HCC with AFP ≥400 ng/mL [8], all of these drugs were tested in "all-comer" trials. The concept of biomarker-driven treatment has been established for several kinds of cancers (*e.g.*, lung cancer and colorectal cancer), resulting in improvement of survival for patients, and should also be a goal for HCC. Many efforts toward biomarker-driven treatment or personalized therapy of HCC guided by molecular profiles obtained from biopsies have been in vain [19-22], which is at least partially ascribed to the complex tumor biology involved. Thus, prognostic markers, like AFP or the progression pattern, representative of the whole tumor load deserve more attention.

The progression pattern of HCC is divided into increase in intrahepatic/extrahepatic tumor size, new intrahepatic lesions, and new extrahepatic lesions according to the BCLC staging system, and new extrahepatic foci are independent predictors of impaired survival. In the current study, we compared the efficacy of apatinib in lung metastases with that in non-lung metastases, including new intrahepatic and new extrahepatic (other than lung) lesions, and demonstrated that apatinib was selectively effective for lung metastases of HCC in terms of better mPFS for the lung *vs.* non-lung metastasis groups; better median OS in the lung *vs.* non-lung metastasis groups; and a trend toward better OS in patients with lung metastasis. Furthermore, the mORR was significantly higher in the patients with lung metastasis only, compared with those with non-lung metastasis only. All of these findings warrant further investigation and confirmation.

Successful treatment of lung metastases of HCC can significantly prolong survival [23]; however, there are no standard programs established for this subgroup of patients. Existing methods can be placed broadly into two categories: locoregional therapies, such as pulmonary metastasectomy and radiofrequency ablation, and systemic drugs, such as conventional chemotherapy and molecular-targeted agents. Locoregional therapies are proven effective in pulmonary metastases after liver transplantation for HCC, and the reported median OS is between 17.4 and 29 months [24-26], but they are not recommended for patients with concurrent pulmonary metastases and intrahepatic lesions, which is the case in the present study. Results from a previous study of chemotherapy in lung metastasis of HCC were disappointing, with a median time to progression of 7.0 weeks (95% CI: 5.8-8.2) and a median OS of 16.6 weeks (95% CI: 10.1-23.1) [27]. Sorafenib is the first-line option for advanced HCC, whether with lung metastases or not; however, Thomas et al [13] and Tian et al [14] reported that

HCC patients with lung metastasis do not benefit from sorafenib, meaning that development of targeted therapy for this subgroup of patients is still urgently needed. Of note, apatinib in the present study was particularly associated with improvement in lung mPFS, response and OS, indicating that lung metastasis of HCC might derive a particular benefit from apatinib.

The biological mechanism underlying the potential association of lung metastases of HCC with apatinib treatment benefit is unclear. However, based on the anatomical characteristics of lung and reported molecular mechanisms that make HCC prone to metastasize to lung, we have several hypotheses on the efficacy of apatinib at that particular site. Once liver cancer cells invade into hepatic veins via arteriovenous or portal-venous shunt, they can spread to the right ventricle and subsequently to the lung. Apatinib, at an appropriate dose, can normalize the abnormal tumor vasculature, potentially reengineer the tumor microenvironment and activate the immune system both in liver and lung, which may decrease the lung metastasis arising from the liver and existing metastatic lung foci [28-31]. It is reported that the circulating VEGF level is associated with the development of lung metastasis in HCC and other kinds of cancer [32,33], and apatinib may prevent that process via its highly selective inhibition of VEGFR-2. These hypotheses will now need to be clarified with basic research.

Various adverse events occurred during apatinib treatment, and the total incidence (any grade) was 93.4%, generally consistent with those reported in previous studies [15,34]. In this study, most side effect reactions were grade 1 or 2, which gradually alleviated and disappeared within 1 or 2 weeks. Grade 3 events (total incidence 8.1%) could be reduced to grade 1 after drug discontinuation or dose reduction, and no grade 4 or 5 adverse events were observed.

Limitations of this study included first, that it was a retrospective, single-arm study with no control group, preventing comparisons with placebo or other targeted agents. Second, a biological link between lung metastasis of HCC and the mechanism of action of apatinib was not illuminated. Third, whether efficacy of apatinib in lung metastasis could be translated into OS benefit for HCC patients was not verified.

Conclusions

In summary, this study demonstrated that apatinib shows significantly better efficacy in terms of mPFS and ORR in HCC patients with lung metastasis than in those with non-lung metastasis. Our findings suggest that, compared with current strategies, apatinib is a better therapeutic option for the treatment of HCC patients with lung metastasis, and prospective randomized controlled trials for confirmation are now required.

Acknowledgements

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Conflict of interests

The authors declare no conflict of interests.

References

1. Liu ZH, Zhang YF, Xu Z. UNC119 promotes the growth and migration of hepatocellular carcinoma via Wnt/beta-catenin signal and TGF-beta/EMT signal pathways. JBUON 2018;23:1717-24.
2. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-2.
3. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-43.
4. Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
5. Cheng AL, Kang YK, Chen Z et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.
6. Bruix J, Qin S, Merle P et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;389:56-66.
7. El-Khoueiry AB, Sangro B, Yau T et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017;389:2492-2502.
8. Gilabert M, Raoul JL. Potential of ramucirumab in treating hepatocellular carcinoma patients with el-

evated baseline alpha-fetoprotein. J Hepatocell Carcinoma 2018;5:91-8.

9. Reig M, Rimola J, Torres F et al. Postprogression survival of patients with advanced hepatocellular carcinoma: rationale for second-line trial design. Hepatology 2013;58:2023-31.
10. Reig M, Bruix J. Pattern of tumor progression in liver cancer: The missing partner in trial design. Hepatology 2015;62:674-6.
11. Uka K, Aikata H, Takaki S et al. Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma. World J Gastroenterol 2007;13:414-20.
12. Zhang SM, Zeng ZC, Tang ZY et al. Prognostic analysis of pulmonary metastases from hepatocellular carcinoma. Hepatol Int 2008;2:237-43.
13. Yau T, Chan P, Ng KK et al. Phase 2 open-label study of single-agent sorafenib in treating advanced hepatocellular carcinoma in a hepatitis B-endemic Asian population: presence of lung metastasis predicts poor response. Cancer 2009;115:428-36.
14. Yang T, Lu JH, Lin C et al. Concomitant lung metastasis in patients with advanced hepatocellular carcinoma. World J Gastroenterol 2012;18:2533-9.
15. Li J, Qin S, Xu J et al. Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Apatinib in Patients With Chemotherapy-Refractory Advanced or Metastatic Adenocarcinoma of the Stomach or Gastroesophageal Junction. J Clin Oncol 2016;34:1448-54.
16. Miao M, Deng G, Luo S et al. A phase II study of apatinib in patients with recurrent epithelial ovarian cancer. Gynecol Oncol 2018;148:286-90.
17. Hu X, Cao J, Hu W et al. Multicenter phase II study of apatinib in non-triple-negative metastatic breast cancer. BMC Cancer 2014;14:820.
18. Rimassa L, Pressiani T, Boni C et al. A phase II randomized dose escalation trial of sorafenib in patients with advanced hepatocellular carcinoma. Oncologist 2013;18:379-80.
19. Zhu AX, Kudo M, Assenat E et al. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. JAMA 2014;312:57-67.
20. Lim HY, Merle P, Weiss KH et al. Phase II Studies with Refametinib or Refametinib plus Sorafenib in Patients with RAS-Mutated Hepatocellular Carcinoma. Clin Cancer Res 2018;24:4650-61.
21. Rimassa L, Assenat E, Peck-Radosavljevic M et al. Tivantinib for second-line treatment of MET-high, advanced hepatocellular carcinoma (METIV-HCC): a final analysis of a phase 3, randomised, placebo-controlled study. Lancet Oncol 2018;19:682-93.
22. Chan SL, Wong AM, Lee K, Wong N, Chan AK. Personalized therapy for hepatocellular carcinoma: Where are we now? Cancer Treat Rev 2016;45:77-86.
23. Cruz RJ, Ranganathan S, Mazariegos G et al. Analysis of national and single-center incidence and survival after liver transplantation for hepatoblastoma: new trends and future opportunities. Surgery 2013;153:150-9.
24. Tomimaru Y, Sasaki Y, Yamada T et al. The significance of surgical resection for pulmonary metastasis from hepatocellular carcinoma. Am J Surg 2006;192:46-51.
25. Nakajima J, Tanaka M, Matsumoto J, Takeuchi E, Fukami T, Takamoto S. Appraisal of surgical treatment for pulmonary metastasis from hepatocellular carcinoma. World J Surg 2005;29:715-8.
26. Zhang T, Lu M, Peng S et al. CT-guided implantation of radioactive 125I seed in advanced non-small-cell lung cancer after failure of first-line chemotherapy. J Cancer Res Clin Oncol 2014;140:1383-90.
27. Lee JO, Kim DY, Lim JH et al. Palliative chemotherapy for patients with recurrent hepatocellular carcinoma after liver transplantation. J Gastroenterol Hepatol 2009;24:800-5.
28. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science 2005;307:58-62.
29. Goel S, Duda DG, Xu L et al. Normalization of the vasculature for treatment of cancer and other diseases. Physiol Rev 2011;91:1071-1121.
30. Hamzah J, Jugold M, Kiessling F et al. Vascular normalization in Rgs5-deficient tumours promotes immune destruction. Nature 2008;453:410-4.
31. Huang Y, Yuan J, Righi E et al. Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. Proc Natl Acad Sci U S A 2012;109:17561-6.
32. Zhan P, Qian Q, Yu LK. Serum VEGF level is associated with the outcome of patients with hepatocellular carcinoma: a meta-analysis. Hepatobiliary Surg Nutr 2013;2:209-15.
33. Xie L, Ji T, Guo W. Anti-angiogenesis target therapy for advanced osteosarcoma (Review). Oncol Rep 2017;38:625-36.
34. Hu X, Cao J, Hu W et al. Multicenter phase II study of apatinib in non-triple-negative metastatic breast cancer. BMC Cancer 2014;14:820.