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Short Report

Liver transplantation for advanced hepatocellular carcinoma after downstaging with consequential lenvatinib, transcatheter arterial chemoembolization and camrelizumab

Wei Peng[1,2], Youwei Wu[1], Xiaoyun Zhang[1], Chuan Li[1], Junyi Shen[1], Weixia Chen[3], Qiu Li[4], Ji Ma[4], Yu Yang[4], Wusheng Lu[1], Zuojin Liu[5], Xin Sun[2], Jiayin Yang[6], Yongjie Zhou[6,*] and Tianfu Wen[1,*]

[1]Division of Liver Surgery, Department of General Surgery, West China Hospital, Sichuan University, Chengdu, China
[2]Chinese Evidence-based Medicine Center, West China Hospital, Sichuan University, Chengdu, China
[3]Department of Radiology, West China Hospital, Sichuan University, Chengdu, China
[4]Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China
[5]Department of Hepatobiliary Surgery, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China
[6]Transplant Center & Laboratory of Liver Transplantation, West China Hospital, Sichuan University, Chengdu, China

Correspondence to: Yongjie Zhou, Transplant Center & Laboratory of Liver Transplantation, West China Hospital, Sichuan University, 37 Guoxue Alley, Wuhou District, Chengdu 610041, China (e-mail: yongjiezhou@scu.edu.cn); Tianfu Wen, Division of Liver Surgery, Department of General Surgery, West China Hospital, Sichuan University, 37 Guoxue Alley, Wuhou District, Chengdu 610041, China (e-mail: wentianfu@scu.edu.cn)

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Introduction

To select patients with hepatocellular carcinoma (HCC) for liver transplantation (LT), Milan criteria are still mainly used worldwide[1]. Several selection criteria that sought to expand the Milan criteria have been proposed and acceptable post-LT survival may be obtained[2]. However, none of the selection criteria challenged advanced HCC with macrovascular invasion. This is generally regarded as a contraindication for LT. Recently, several studies showed that combinations of locoregional and systemic treatment could significantly improve tumour response and overall survival for patients with advanced HCC[3–5]. This included promising results of lenvatinib, transcatheter arterial chemoembolization (TACE) and programmed cell death protein 1 (PD-1) inhibitor (LEN-TAP) for advanced HCC[6]. With the improvement of combination therapy, the authors wondered whether LT could serve as another option for patients with advanced HCC after successful downstaging. The present study described the perioperative and postoperative outcome of patients who opted for LT when they failed to receive salvage liver resection due to decompensated liver function after successful downstaging.

Methods

LEN-TAP is an investigator-initiated trial that was designed to investigate efficacy and safety of salvage liver resection after conversion therapy of lenvatinib, TACE and PD-1 inhibitor in patients with unresectable HCC[7]. The study protocol was approved by ethics committee of West China Hospital (2020-836) and the study was registered at ClinicalTrial.gov (NCT04997850). Details of LEN-TAP study design are available in *Supplementary material*. Clinical data of patients who opted for LT when they failed to receive salvage liver resection due to decompensated liver function after successful downstaging were reviewed and analysed. LT was suggested after several multidisciplinary team meetings based upon the following considerations: advanced stage disease was downstaged within Milan criteria and complete tumour necrosis was found[8] on enhanced computed tomography; and decompensated liver function and high risk of post-hepatectomy liver failure. Additional methods are shown in the supplementary file.

Results

Between October 2020 and March 2022, 142 patients were enrolled in the LEN-TAP trial, and 71 patients received the triple combination therapy. According to LEN-TAP study protocol, 62 (87.3%) patients were amenable to receive salvage liver resection after the conversion therapy. Finally, 42 (59.2%) patients successfully received salvage liver resection whereas 4 patients failed to received salvage liver resection due to decompensated liver function (*Fig. S1*). Finally, two patients received marginal donor LT and one patient received living donor LT. All these three patients had advanced HCC with portal vein tumour thrombus. Baseline characteristics and perioperative outcomes are shown in *Table S1*.

Images obtained before therapy, before LT and one year after LT, and pathological response of explanted liver and alpha-fetoprotein trends are shown in *Fig. 1*. All three patients remained alive with stable graft function and without tumour recurrence or metastasis (*Fig. 1*). Two patients had uneventful postoperative

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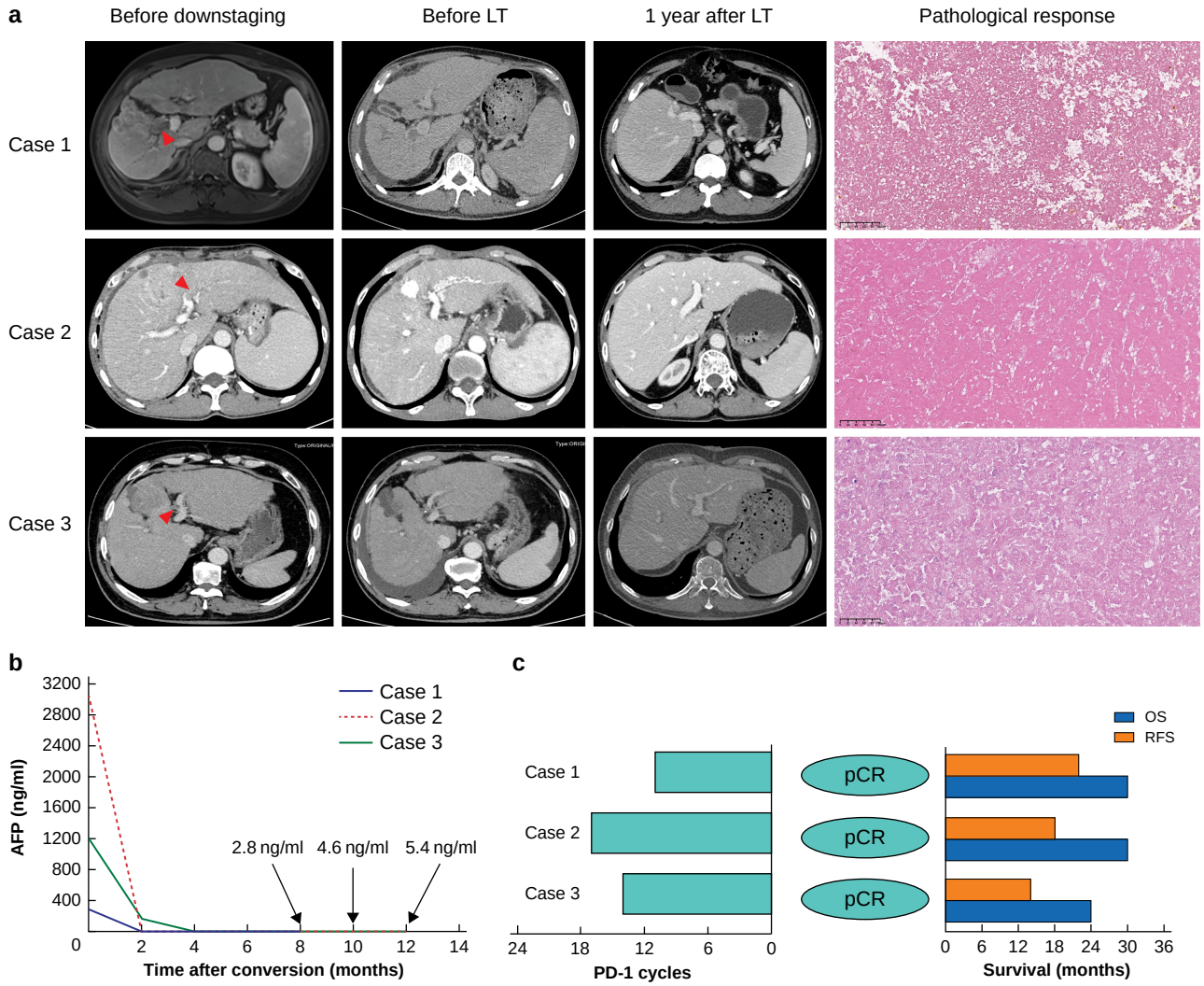

Fig. 1 Outcome for patients who underwent LT in LEN-TAP trial

a Radiological and pathological response for three patients who underwent LT. Target lesion and tumour thrombus (indicated by red arrows) necrosis and ascites were found after treatment; tumour-free images were obtained one year after LT; no residual tumour cells were found in explanted liver. **b** AFP trends between initiation of LEN-TAP therapy and pre-transplant. AFP decreased dramatically in these three patients after downstaging therapy. **c** Programmed cell death protein 1 inhibitor cycles before transplant, pathological response and survival time for patients received LT. LT, liver transplantation; LEN-TAP, lenvatinib, transarterial chemoembolization and PD-1 inhibitor therapy; AFP, alpha-fetoprotein; RFS, recurrence-free survival; OS, overall survival; pCR, pathological complete response.

recoveries and one patient experienced acute rejection after LT. Timely administration of steroid pulse therapy and adjustment of the immunosuppression drug dosage led to a successful recovery.

Discussion

Combination of locoregional and systemic therapies has shown synergistic effects and plays a significant role in conversion therapy for unresectable HCC. The purpose is salvage resection for the tumour[9]. Several retrospective studies reported promising response rates and salvage resection rate following triple combination of TACE, tyrosine kinase inhibitor (TKI) and PD-1 inhibitor for unresectable HCC[10,11]. The authors' pilot study and interim results of LEN-TAP trial showed promising tumour response and conversion resection rate[6,7]. Here, the authors reported the outcomes of salvage LT after successful downstaging by triple combination of lenvatinib, TACE and PD-1 inhibitors for advanced HCC.

Due to the potential induction of immune-related hepatitis and potentially fatal allograft rejection, the use of immunotherapy is controversial in the pre-transplant setting[12]. Therefore, aggressive induction immunosuppression with intravenous methylprednisolone and basiliximab was implemented prior to LT. The occurrence of acute rejection may be related to the relatively short interval between the last dose of PD-1 inhibitor and LT. The timing of deceased donor LT is uncertain, which complicates the decision of when to discontinue immunotherapy before LT. Studies have shown that discontinuing immunotherapy for at least 3 months prior to LT may be helpful to prevent acute rejection and graft loss[13].

Continuing systemic therapy has been the standard of care for these patients. Then, disease progression usually occurs within 1–1.5 years after achieving a response[14]. For patients with resectable HCC it is generally accepted that complete removal of tumour provides the best opportunity of cure and offers favourable survival[15]. It is reasonable to believe that salvage LT for patients who were not feasible for salvage liver resection after successful downstaging might provide an acceptable post-LT survival. Further prospectively designed studies are needed to provide solid evidence.

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Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Wei Peng (Conceptualization, Data curation, Methodology, Writing—original draft, Writing—review & editing), Youwei Wu (Methodology, Software, Validation, Writing—review & editing), Xiaoyun Zhang (Investigation, Writing—review & editing), Chuan Li (Investigation, Writing—review & editing), Junyi Shen (Data curation, Investigation, Writing—review & editing), Weixia Chen (Supervision, Writing—review & editing), Qiu Li (Project administration, Supervision, Writing—review & editing), Ji Ma (Writing—review & editing), Yu Yang (Methodology, Writing—review & editing), Wu-sheng Lu (Data curation, Supervision, Writing—review & editing), Zuojin Liu (Data curation, Investigation, Writing—review & editing), Xin Sun (Investigation, Methodology, Project administration), Jiayin Yang (Supervision, Writing—review & editing), Yongjie Zhou (Conceptualization, Formal analysis, Funding acquisition, Writing—review & editing), and Tianfu Wen (Conceptualization, Funding acquisition, Investigation, Project administration, Writing—original draft, Writing—review & editing)

References

1. Brown ZJ, Tsilimigras DI, Ruff SM, Mohseni A, Kamel IR, Cloyd JM *et al.* Management of hepatocellular carcinoma: a review. *JAMA Surg* 2023;**158**:410–420
2. Li J, Yan LN, Yang J, Chen ZY, Li B, Zeng Y *et al.* Indicators of prognosis after liver transplantation in Chinese hepatocellular carcinoma patients. *World J Gastroenterol* 2009;**15**:4170–4176
3. Zhu HD, Li HL, Huang MS, Yang WZ, Yin GW, Zhong BY *et al.* Transarterial chemoembolization with PD-(L)1 inhibitors plus molecular targeted therapies for hepatocellular carcinoma (CHANCE001). *Signal Transduct Target Ther* 2023;**8**:58
4. Peng Z, Fan W, Zhu B, Wang G, Sun J, Xiao C *et al.* Lenvatinib combined with transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma: a phase III, randomized clinical trial (LAUNCH). *J Clin Oncol* 2023;**41**:117–127
5. Chiang CL, Chiu KWH, Chan KSK, Lee FAS, Li JCB, Wan CWS *et al.* Sequential transarterial chemoembolisation and stereotactic body radiotherapy followed by immunotherapy as conversion therapy for patients with locally advanced, unresectable hepatocellular carcinoma (START-FIT): a single-arm, phase 2 trial. *Lancet Gastroenterol Hepatol* 2023;**8**:169–178
6. Peng W, Zhang X, Li C, Zhu X, Li Q, Chen W *et al.* Programmed cell death protein 1 and tyrosine kinase inhibition plus transcatheter arterial chemoembolization of advanced hepatocellular carcinoma. *Br J Surg* 2023;**110**:746–748
7. Xiaoyun Z, Zhu X, Feng X, Han W, Yan ML, Xie F *et al.* 715P the safety and efficacy of lenvatinib combined with TACE and PD-1 inhibitors (Len-TAP) *versus* TACE alone in the conversion resection for initially unresectable hepatocellular carcinoma: interim results from a multicenter prospective cohort study. *Ann Oncol* 2022;**33**:S870
8. Yao FY, Fidelman N, Mehta N. The key role of staging definitions for assessment of downstaging for hepatocellular carcinoma. *Semin Liver Dis* 2021;**41**:117–127
9. Sun HC, Zhou J, Wang Z, Liu X, Xie Q, Jia W *et al.* Chinese expert consensus on conversion therapy for hepatocellular carcinoma (2021 edition). *Hepatobiliary Surg Nutr* 2022;**11**:227–252
10. Qu WF, Ding ZB, Qu XD, Tang Z, Zhu GQ, Fu XT *et al.* Conversion therapy for initially unresectable hepatocellular carcinoma using a combination of toripalimab, lenvatinib plus TACE: real-world study. *BJS Open* 2022;**6**:zrac114
11. Wu JY, Yin ZY, Bai YN, Chen YF, Zhou SQ, Wang SJ *et al.* Lenvatinib combined with anti-PD-1 antibodies plus transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: a multicenter retrospective study. *J Hepatocell Carcinoma* 2021;**8**:1233–1240
12. Nordness MF, Hamel S, Godfrey CM, Shi C, Johnson DB, Goff LW *et al.* Fatal hepatic necrosis after nivolumab as a bridge to liver transplant for HCC: are checkpoint inhibitors safe for the pretransplant patient? *Am J Transplant* 2020;**20**:879–883
13. Schnickel GT, Fabbri K, Hosseini M, Misel M, Berumen J, Parekh J *et al.* Liver transplantation for hepatocellular carcinoma following checkpoint inhibitor therapy with nivolumab. *Am J Transplant* 2022;**22**:1699–1704
14. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-Y *et al.* IMbrave150: updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo) + bevacizumab (bev) *versus* sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). *J Clin Oncol* 2021;**39**:267–267
15. Lau WY, Lai EC. Salvage surgery following downstaging of unresectable hepatocellular carcinoma—a strategy to increase resectability. *Ann Surg Oncol* 2007;**14**:3301–3309