Viewpoint

Conversion surgery for hepatocellular carcinoma in the new era of targeted and immune checkpoint inhibitor therapies

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Submitted Sep 02, 2020. Accepted for publication Sep 12, 2020.
doi: 10.21037/hbsn-20-693
View this article at: http://dx.doi.org/10.21037/hbsn-20-693

In the recent decade, systemic treatment of unresectable hepatocellular carcinoma (uHCC) with targeted and immune checkpoint inhibitors (ICIs) has achieved great progress. In the SHARP study conducted 12 years ago, sorafenib, the first systemic drug approved by the Food and Drug Administration (FDA) for advanced HCC, increased the median overall survival (mOS) from 7.9 to 10.7 months (1). This year, in the newly-released results from phase III IMbrave 150 study, the combination of anti-programmed death ligand 1 (PD-L1) inhibitor atezolizumab and anti-vascular endothelial growth factor (VEGF) drug bevacizumab has significantly increased the mOS and median progress free survival (mPFS) compared to sorafenib group (2). In another combination that attracted much attention, a phase Ib study for uHCC found that lenvatinib plus pembrolizumab achieved a mOS of 22.0 months (3). Based on promising phase 1b result, the phase III LEAP-002 study (NCT03713593) of lenvatinib plus pembrolizumab versus lenvatinib plus placebo as first-line treatment of uHCC is ongoing. However, although significant progress has been made, long-term survival in uHCC patients achieved by targeted and/or ICIs therapies is still very rare and patients surviving over 5 years are only found in limited case reports.

Radical therapies (hepatic resection, liver transplantation and ablation in well-selected patients) are still the only curative-intent treatments for HCC. In patients who meet guidelines and undergo resection, 5-year survival rate with these modalities is over 60% (4). However, just only 10–30% of HCC patients are ideal candidates for liver resection, and 70% of them will experience recurrence within 5 years of resection (4).

Taking these data together, a very straightforward conclusion will be arrived at; if more uHCC patients can have curative therapy after conversion surgery, and less patients develop recurrence by adjuvant therapies, significantly more HCC patients will experience long-term survival or even cure. At new era, targeted drugs, ICIs or its combination therefore bring new hope for both conversion surgery and adjuvant therapy.

Conversion surgery in HCC is not a new concept. Tang *et al*. reported that from 1958 to 2003, 139 (12.8%) out of 1085 uHCC patients were converted to "downstaging resection", and their 5-year survival rate reached 48.7% (5). The conversion therapies included hepatic artery ligation (HAL), hepatic artery cannulation with chemotherapeutic infusion (HAI), radiotherapy and radioimmunotherapy or various combinations therein. Fan *et al*. from the same institute reported a conversion rate of 18.1% (65 out of 360) in uHCC patients by transarterial chemoembolization (TACE), and a 5-year survival rate was 56.0% (6). Excepted hepatectomy, downstaging resection of uHCC for liver transplantation is also promising strategy (7).

The objective response rate (ORR) is pivotal for the conversion surgery. ORR of TACE for intermediate-stage HCC is reported to be 52.5% (4); compare to TACE, the ORR of sorafenib in SHARP study was only 2% [7 partial responses (PR) out of 299 advanced HCCs]; later, the IMbrave 150 study, reported an ORR of sorafenib at 13.3% [3 complete responses (CR) and 18 PR out of 158

Table 1 Reported conversion surgery of HCC following TKI/ICI in the literature

	References	Case number	Combined therapies
Sorafenib			
1	*World J Gastroenterol* 2011;17:2255	1	Gemcitabine plus oxaliplatin
2	*Int J Hepatol* 2011:791013	2	
3	*Liver Int* 2011;31:740	2	
4	*Int Surg* 2015;100:908	1	TACE + RT
5	*Gastroenterol* 2015;8:300	1	RT
6	*Gan To Kagaku Ryoho* 2015;42:1638	1	TAE/TACE
7	*Anticancer Res* 2018;38:501	2	
8	*Exp Clin Transplant* 2018;16:227	2/5	Convert to LT
9	*Gan To Kagaku Ryoho* 2020;47:502	1	TACE/TAI
10	*Per Med* 2020;17:83	2	
Lenvatinib			
1	*Onco Targets Ther* 2019;12:7355	1	PD-1
2	*Anticancer Res* 2019;39:5695	1	
3	*Liver Cancer* 2020;9:358	1	
Regorafenib			
1	*Clin J Gastroenterol* 2020;13:428	1	Following sorafenib

TACE, transarterial chemoembolization; RT, radiotherapy; LT, liver transplantation; TAI, transarterial infusion; PD-1, anti-programmed cell death protein 1.

uHCCs] according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Four years after its approval by FDA, sporadic cases of conversion surgery following sorafenib began to be reported (*Table 1*). Over the last 13 years, there are only few reports of conversion surgery following sorafenib. The ORR of lenvatinib in the REFLECT study was 24.1% (6 CR and 109 PR out of 478 uHCCs) (8). Lenvatinib received FDA approval for the first line treatment of uHCC in 2018, so far there have been 3 conversion surgeries reported (*Table 1*). There was a case report that PD-1 inhibitor could as a downstaging therapy for liver transplantation for uHCC (9). The ORR of atezolizumab plus bevacizumab in IMbrave 150 study was 33.2% (33 CR and 75 PR out of 325 uHCCs) (2), and the ORR of lenvatinib plus pembrolizumab in phase Ib study reached as high as 46% (11 CR and 35 PR out of 100 uHCCs) (3). On 29th May 2020, FDA has approved Atezolizumab plus bevacizumab for the first line treatment of uHCC.

Both the mOS and the ORR of these new tyrosine kinase inhibitor (TKI) + ICI treatments in HCC have reached the similar level as TACE, we should therefore be confident that more and more conversion surgeries can be expected with these therapies. In the 2020 ASCO (American Society of Clinical Oncology) Conference, Sun *et al.* reported that out of 60 consecutive uHCC patients, 11 patients (18.3%) were converted to resectable through different TKI plus anti-PD-1 therapy, and 9 patients underwent hepatectomy. Notably, among 9 patients, there were 5 PR and no CR evaluated before surgery, there were 3 instances stable diseases (SD) with one patient experiencing progressive disease (PD) (RECIST v1.1), but the uHCC was still converted to resectable and hepatectomy was achieved successfully (10).

In clinical trials of target drugs and ICIs, OS is often the main focus and primary endpoint, because PFS, ORR and time to progression (TTP) are regarded as not consistently predictive of OS in HCC. This makes sense from the simple medical oncological viewpoint. While from the multidisciplinary viewpoint, longer term survival or even

curative outcome can be achieved through the combination of different therapeutic modalities. In this setting, ORR of target drugs and ICIs in systemic treatment of uHCC can be potentially very important. Considering the fact that the TKI + ICI treatments in uHCC has led to the ORR and mOS close to TACE and other traditional therapies like HAL + HAI, the systemic application of targeted drugs and/or ICIs in the conversion surgery of uHCC should be seriously considered, and well-designed randomized control trials (RCTs) should be organized to address this issue We hope another 10 to 20 percent of uHCC could be converted to curative HCC resection in the new era of targeted and immune checkpoint inhibitor therapies. In the future, we anticipate the results of immunotherapy 3.0 era (PD-1/PD-L1+TKI/VEGF + locoregional therapy) for uHCC (NCT03778957/EMERALD-1; NCT04246177/LEAP-012; NCT04224636/DEMAND). Identification and enrichment of target patients (PD-L1 positive, good ECOG score or local advanced stage) need for further investigation.

Acknowledgments

We thank Dr. Alex Gordon-Weeks from Nuffield Department of Surgical Sciences, University of Oxford for his careful reviewing and constructive suggestions to the manuscript.
Funding: LZ is supported by the National Natural Fund of China (No. 30801383 and No. 81472713).

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/hbsn-20-693). HZ serves as an unpaid editorial board member of *Hepatobiliary Surgery and Nutrition*. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Zhao L, Zhao H. Conversion surgery for hepatocellular carcinoma in the new era of targeted and immune checkpoint inhibitor therapies. HepatoBiliary Surg Nutr 2020;9(6):809-811. doi: 10.21037/hbsn-20-693

