OncoTargets and Therapy

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CASE REPORT

Lenvatinib combined nivolumab injection followed by extended right hepatectomy is a feasible treatment for patients with massive hepatocellular carcinoma: a case report

This article was published in the following Dove Press journal:
OncoTargets and Therapy

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Abstract: Hepatocellular carcinoma (HCC) is a highly aggressive malignant tumor. The survival of advanced HCC is very poor. In this case study, we describe the treatment of a 69-year-old woman diagnosed with massive hepatocellular carcinoma, the use of lenvatinib in combination with nivolumab injection in the preoperative adjuvant treatment of advanced massive hepatocellular carcinoma, and the final taking extended right hepatectomy. Molecular targeted drugs and immunotherapy controlled patient's condition to create time and conditions for surgery. After surgery, AFP was greatly reduced, no recurrence of the residual liver and no metastasis in the distance. This treatment is the gospel of patients with advanced liver cancer.

Keywords: HCC, lenvatinib, nivolumab injection, hepatectomy, combination therapy

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Introduction

The characteristics of hepatocellular carcinoma treatment are the coexistence of multiple methods and disciplines. For the time being, surgical treatment of HCC is the most important means for long term survival of HCC patients.[1] It is extremely difficult to make a surgical choice for massive hepatocellular carcinoma with cirrhosis, and it is likely to cause major hemorrhage and postoperative liver failure due to insufficient residual liver volume.[2] With the two major trials of SHARP and Oriental, Sorafenib has opened a new era of advanced HCC targeted therapy.[3,4] Lenvatinib (Eisai Europe Ltd. the United Kingdom) is an orally administered, multitargeted tyrosine kinase inhibitor that selectively inhibits VEGFR1–3, fibroblast growth factor receptor (FGFR) 1–4, PDGFRα, RET, and KIT. Lenvatinib has been shown to be safe and effective in the treatment of differentiated thyroid cancer and advanced renal cell carcinoma.[5] Nivolumab injection (Bristol-Myers Squibb Holdings Pharma, Ltd. United States of America) is a fully monoclonal antibody to disrupts PD-1 immune checkpoint signaling and exhibits significant clinical activity in unresectable or metastatic melanoma, refractory non-small cell lung carcinoma, and advanced renal cell carcinoma.[6] Lenvatinib and nivolumab injection has been approved by the FDA as first- and second-line treatment for advanced HCC.

The choice of the way to treat refractory HCC is a breakthrough point that is sought by the majority of clinical and scientific researchers. In this case, we report a case of massive hepatocellular carcinoma undergoing extended right hepatectomy

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http://doi.org/10.2147/OTT.S217123

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after targeted drug combination immunotherapy. As far as we know, this is the first reported case.

Case presentation

A 69-year-old woman with a bodyweight of 51 kg was found a liver lesion at a local hospital in September 2018. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a large 14.5×10.9 cm mass in the liver. We regarded the lesion as massive hepatocellular carcinoma. After failing to take TACE treatment on September 11, 2018, she took sorafenib from September 11th to 18th. During the medication, she developed vomiting, hair loss, and thrombocytopenia and then transferred to the departments of liver surgery, the First Affiliated Hospital of USTC (Hefei, China). The patient was accompanied by fever during the course of the disease, and there was no special discomfort. She has a history of hepatitis B for many years without medication and other treatments. Physical examination: Percussion tenderness over hepatic region, no other special. Laboratory examination: HBsAg (+), HBeAg (+), HBcAb (+), other negative, AFP:39684ng/mL, the Child-Pugh grade 8 points (stage B). On September 26, 2018, the abdominal enhancement CT revealed that a large round-like mixed density mass in the liver, with a maximum section of 15.0×10.8 cm (Figure 1A). In the enhanced arterial phase, multiple tortuous tumor vessels were seen in the lesion, and multiple small lymph nodes were seen in the hepatic portal and posterior peritoneal.

We informed patient and her relatives about the treatment options and alternatives, we started treatment with lenvatinib (8mg orally every day) on September 28, 2018. Regular outpatient review, enhancement CT on October 30, 2018: a liver lesion of 14.0×10.0 cm in size, From November 22, 2018, to March 05, 2019, patients with lenvatinib (8mg orally every day) combined with nivolumab injection (140mg intravenously every 2 weeks) treatment. Changes in tumor diameter, platelet, AFP and the maximum cross-sectional square of necrosis during the half-year period of treatment (Figure 1B, Table 1). Positron emission tomography (PET)-CT showed no distant metastasis.

On March 15th, she visited our hospital again, AFP: 167899ng/mL, Primovist MRI: The liver revealed a lesion with a large piece of long T1 and a slightly longer T2 signal, about 13.0×8.5 cm, and see more than one satellite nodule (Figure 1C), this mass can also be seen on CT. We received the results of 3D visualization based on the CT image using the software (Mixed reality Surgical Planning Simulation System) and performed the extended right hepatectomy to obtain the remnant liver volume (Figure 2A and B, Table 2).

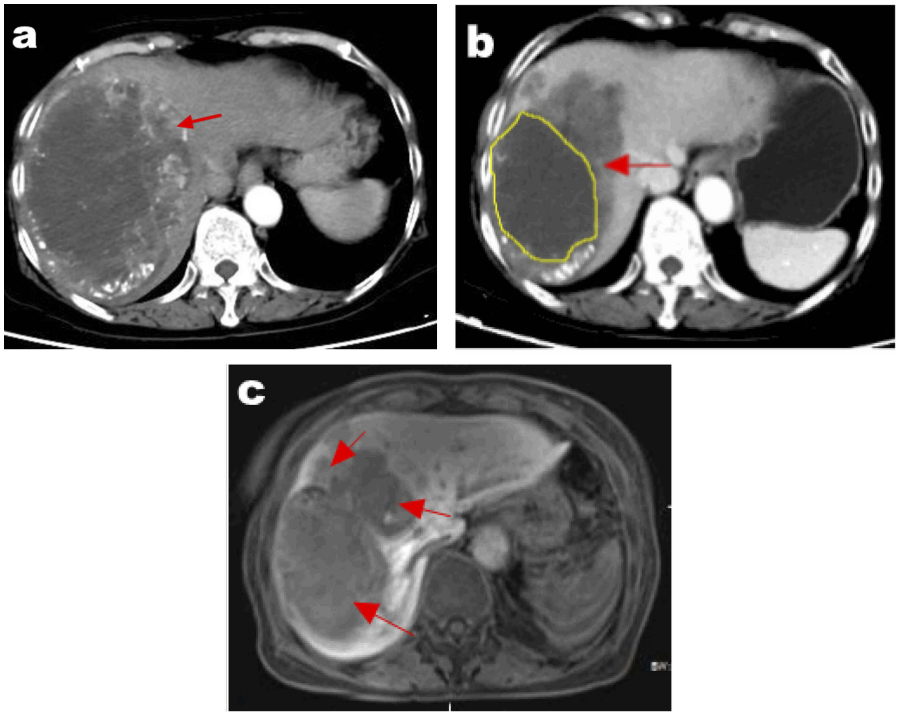

Figure 1 Preoperative abdominal enhancement CT and Primovist MRI revealed a large liver space-occupying lesion. (**A**) CT arterial phase image: a heterogeneously enhanced mass located in the liver (arrow) (2018–09). (**B**) We circled the largest cross-sectional area of liver tumor necrosis (arrow) (2019–02). (**C**) Preoperative Primovist MRI image, multiple lesions (arrow), maximum tumor size:13.0×8.5 cm (2019–03).

Table 1 Changes in tumor diameter, platelet, AFP, and necrotic area during treatment

Year/month	Tumor diameter (cm)	Platelet (10^9/L)	AFP (ng/mL)	S_{max} (necrotic area) § (cm^2)
2018/09	15	195	39,684	39.47
2018/10	14			40.64
2018/12	13.5		77,051	41.52
2019/02	12	62	86,504	45.65
2019/03	13	136	167,899	48.84
2019/04		134^	26,513^	
2019/06		116^	>1210^	

Notes: S_{max} (necrotic area) =maximum cross-sectional square of necrosis area. §Relative value obtained using a CT image reader. Postoperative index. ^Postoperative index.

The patient and her relativesstrongly demand surgery, we actively inform the surgical risk and possible prognosis and sign a written informed consent form. After discussion in the department, it is considered that the operation is risky and liver failure may occur. In order to meet the patient's request, it is decided to completely remove the lesion and retain the left lateral lobe to reduce the load and strengthen postoperative management. In addition, postoperative pathology can determine whether microvascular invasion is combined and guide the next treatment. The extended right hepatectomy and cholecystectomy were performed on March 25. During the operation, the giant tumor was mainly located in the right liver and invaded into the S4. The size is about 12.0×10.0 cm, solid and soft, with mild adhesion to the diaphragm (Figure 3A). After the tumor was dissected: the section showed a size of 12.5×11.0×10.0 cm gray yellow gray red tender nodules, a large number of necrotic tissue in the middle, and see more than one satellite nodule, the larger diameter of 3.0 cm (Figure 3B). The pathological report showed that the cancer cells were arranged in a flaky arrangement, and the nuclear fission was easy to see and had microvascular invasion (Figure 3C). Diagnosed as moderate to poorly differentiated hepatocellular carcinoma. After the operation, continue oral lenvatinib, regular review CT to monitor tumor recurrence.

Discussion

Primary liver cancers mainly refer to malignancies that originate from hepatocytes hepatocellular carcinoma (HCC), which account for the majority of PLC, it is estimated that 50% of liver cancer cases and deaths worldwide occur in China.[7] At present, the treatment methods of liver cancer mainly include radical hepatectomy, liver transplantation, local ablation, chemoembolization, and transcatheter therapies, targeted therapy, and immunotherapy. For the treatment of refractory advanced liver cancer, the above treatment methods are required to complement each other and comprehensive treatment. The REFLECT trial showed that patients with the lenvatinib group had better overall survival (OS) and progression-free survival (PFS) than the sorafenib group and the guidelines have

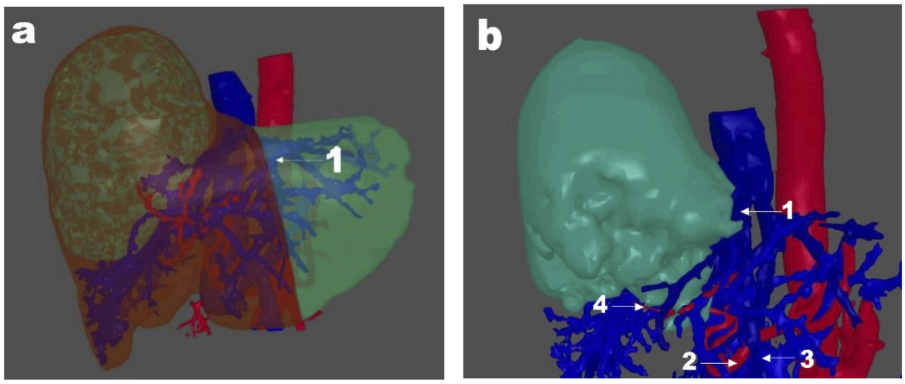

Figure 2 3D visualization pictures. (**A**) We pre-cut along the right side of the left hepatic vein (1) based on the 3D visualization results. (**B**) 3D visualization clearly reconstructs the hepatic vein (1), hepatic artery (2), portal vein (3), and tumor feeding artery (4).

Table 2 3D reconstruction data and calculation of future liver volume ratio

Date	PELV (no tumor) (mL)	FLV (mL)	SLV (mL)	Tumor volume (mL)	FLV/SLV (%)
2018/09/25	1,092.72	219.28	1072.02	898.06	20.45
2018/10/29	988.16	220.20	1061.97	947.94	20.73
2018/12/24	940.04	226.20	1061.97	763.55	21.30
2019/02/16	865.00	229.59	1053.93	758.24	21.78
2019/03/21	810.03	230.83	1043.87	766.05	22.11

Notes: BSA=BW (kg)$^{0.425}$×BH (cm)$^{0.725}$×0.007184. Height (BH):160cm, weight (BW): reduced from 51 kg to 48 kg within six months.
Abbreviations: PELV, predicted excisional liver volume; FLV, future liver volume; SLV, standard liver volume =706.2×BSA(m^2) +2.4.

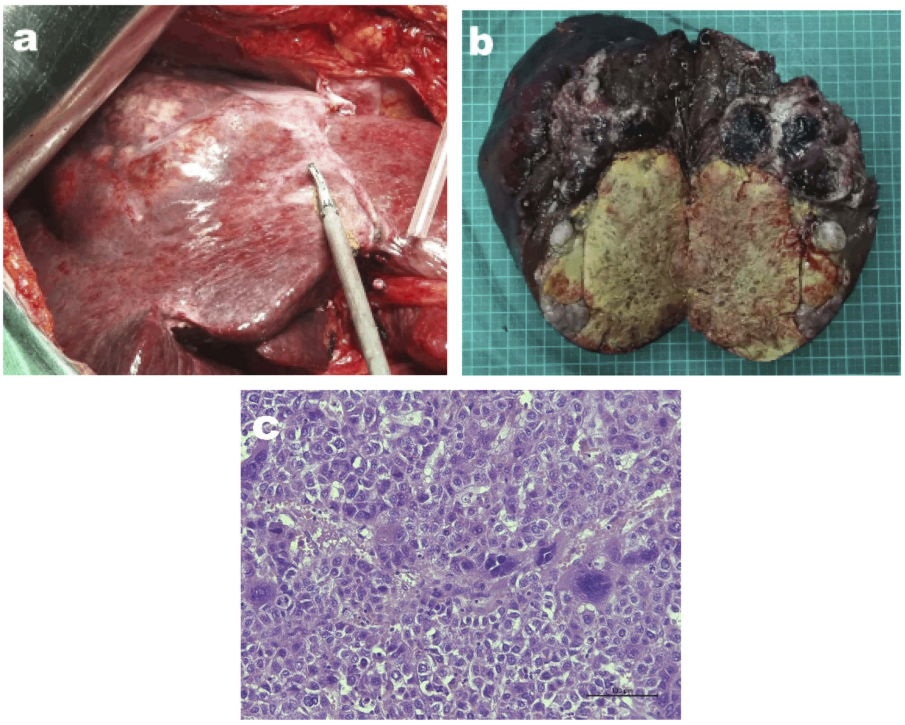

Figure 3 Intraoperative photos, postoperative tumor section and pathological examination pictures. (**A**) Massive hepatocellular carcinoma, Liver resection by Ultrasonic Harmonic Scalpel. (**B**) The section revealed a carcinoma with a large number of necrotic tissues. (**C**) Pathological diagnosis: massive hepatocellular carcinoma, ×100.

recommended it as a first-line treatment for unresectable HCC.[5,8,9] On September 23, 2017, the FDA approved the second-line treatment of late HCC with nivolumab injection.

Neoadjuvant chemotherapy, which reduced tumor burden by preoperative chemotherapy, thereby improving the surgical R0 resection rate and prolonging the survival of patients. At present, neoadjuvant chemotherapy has been widely used in the preoperative treatment of breast cancer, cervical cancer, colorectal cancer, esophageal cancer, and gastric cancer. Angiogenesis and immunosuppression constitute the tumor microenvironment, while VEGF/VEGFR pathway can participate in the regulation of tumor microenvironment immune status.[10] Lenvatinib in combination with nivolumab injection, normalizes vascularization by blocking VEGF pathway, remodels tumor microenvironment, and the lymphocytes are more transmitted to the tumor site, and the inhibitory effect on the tumor microenvironment can be relieved.[11] The combined use of the drug makes the curative effect better.

According to the Barcelona Clinic Liver Cancer (BCLC) staging system, systemic therapies are the standard treatment for BCLC stage C HCC.[8] Referring to the experience of other neoadjuvant chemotherapy for malignant tumors and the pathophysiology of the tumor microenvironment, in this case, lenvatinib combined nivolumab injection before surgery. Adverse events included hand-foot syndrome, hypertension, and anorexia, but these were well controlled. During the treatment period of half a year, the maximum cross-sectional area of giant liver cancer

became smaller, the central enhancement was reduced, and large area necrosis occurred. The combination treatment showed great efficacy and safety while earning patients a chance of radical resection. In our surgery, the liver was freed and the adhesion between the giant tumor and the diaphragm was separated. The first hepatic portal and the second hepatic portal were dissected in turn, only the left lateral lobe of the liver was retained, and the remaining liver including tumors was resected, future liver volume (FLV)/standard liver volume (SLV) is about 22%. The operation was successful and the AFP (26513ng/mL) was greatly reduced. There was no liver failure and recurrence during the postoperative follow-up.

Conclusion

We report a case of massive HCC undergoing extended right hepatectomy after adjuvant treatment with a combination of lenvatinib and nivolumab injection. For advanced liver cancer patients who cannot undergo one-stage radical hepatectomy, targeted therapy combined with immunotherapy provides a new idea and is a safe and effective treatment. However, prospective randomized clinical studies that require larger samples are further confirmed.

Acknowledgment

The authors are grateful to the patient, who gave her written informed consent for publication.

Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Kokudo T, Hasegawa K, Yamamoto S, et al. Surgical treatment of hepatocellular carcinoma associated with hepatic vein tumor thrombosis[J]. Journal of Hepatology. 2014;61(3):583–588. doi:10.1016/j.jhep.2014.04.032
2. Schindl JM. The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection[J]. *Gut*. 2005;54(2):289–296. doi:10.1136/gut.2004.046524
3. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *New Engl J Med*. 2008;359(4):378–390. doi:10.1056/NEJMoa0708857
4. 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(1):25–34. doi:10.1016/S1470-2045(08)70285-7
5. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet*. 2018;391(10126):1163–1173. doi:10.1016/S0140-6736(18)30207-1
6. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab injection in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*. 2017;389(10088):2492–2502. doi:10.1016/S0140-6736(17)31046-2
7. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87–108. doi:10.3322/caac.21262
8. European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. [J]. Journal of hepatology. 2012;56(4). doi:10.1016/j.jhep.2011.12.001
9. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. [J]. Hepatology (Baltimore, Md.). 2018;67(1). doi:10.1002/hep.29086
10. Wallin JJ, Bendell JC, Funke R, et al. Atezolizumab in combination with bevacizumab enhances antigen-specifific T-cellmigration in metastatic renal cell carcinoma. *Nat Commun*. 2016;7:12624. doi:10.1038/ncomms12624
11. Hegde PS, Wallin JJ, Mancao C. Predictive markers of anti-VEGF and emerging role of angiogenesis inhibitors as immunotherapeutics [J]. Seminars in cancer biology. 2018;52(Pt2):117-124. doi:10.1016/j.semcancer.2017.12.002

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