Multimodal combination regimen for a patient with advanced huge hepatocellular carcinoma: a case report

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Background: Hepatocellular carcinoma (HCC) is a highly malignant tumor of the digestive system with a poor prognosis. Huge HCC, a subtype characterized by tumors measuring at least 10 cm in diameter, often presents with macrovascular invasion, satellite nodules, metastases, and other aggressive characteristics, posing significant challenges for treatment. The era of combined targeted therapy and immunotherapy has brought new hope to patients with advanced HCC. The development of innovative combination medication regimens for HCC is a current area of intense clinical research interest. We are trying to explore new combination therapies based on target-immunity combination therapy in the hope of better-benefiting patients with advanced huge HCC.

Case Description: We present a patient with Barcelona Clinical Liver Cancer Stage C huge HCC who was treated with combined targeted therapy and immunotherapy as the primary therapeutic regimen, supplemented with tegafur long-term metronomic chemotherapy, as well as specialized adjuvant therapy such as thymosin, bisphosphonates, antiviral medication, and vitamin C supplementation. The tumor size was significantly reduced and microwave ablation was performed, after which, the patient was kept on the combination regimen, resulting in a partial response (PR), and maintaining PR without disease progression for 32 months.

Conclusions: The combination regimen may enhance advanced huge HCC treatment and provide a new multimodal drug strategy for HCC.

Keywords: Huge hepatocellular carcinoma (huge HCC); targeted therapy; immunotherapy; multimodal combination regimen; case report

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor and the third leading cause of cancer death globally, and it is a major hazard to human health (1). Hepatitis B virus (HBV) infection has long been associated with chronic inflammation and liver damage, making it a key risk factor for hepato-carcinogenesis. Patients with HCC are usually diagnosed at an advanced stage, which makes treatment more challenging. This is because of the absence of obvious clinical signs in early-stage HCC patients and the inadequacy of early screening and diagnostic techniques. About 20% of patients have huge HCC, >10 cm in diameter. Compared with small HCC, huge HCC has a poorer prognosis due to a higher likelihood of developing macrovascular invasion, local invasion, or extrahepatic metastasis (2). Therefore, patients with huge HCC often fail to receive extensive surgery, liver transplantation, local radiofrequency ablation, or other curative procedures. The standard treatment procedure for huge HCC is still unclear, despite notable advances in recent decades (3).

As targeted therapy development progressed, drugs such as lenvatinib, apatinib and donafenib were introduced to the market, improving the prognosis of HCC patients to some extent. Targeted therapy using multi-targeted tyrosine kinase inhibitors (TKIs) can successfully suppress HCC cell line proliferation and cause apoptosis, resulting in anticancer benefits. Their ability to block the vascular endothelial growth factor receptor (VEGFR) pathway is significant in treating highly vascularized HCC (4). The development of immunotherapy has led to new opportunities in treating HCC, with combination therapy based on immune checkpoint inhibitors (ICIs) improving the clinical outcome of HCC patients. As a first-line treatment, combination treatments using ICIs and anti-VEGFR antibodies are advised for advanced HCC (5). Thus, investigating novel combination regimens to improve efficacy in HCC has emerged as a popular area of study. This study describes the promising efficacy of a new multimodal combination therapy in a patient with advanced large HCC. We present this case in accordance with the CARE reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-24-91/rc).

Highlight box

Key findings

- The new multimodal combination therapy in a patient with advanced large hepatocellular carcinoma (HCC) presents a promising efficacy.

What is known and what is new?

- Advanced huge HCC has a poor prognosis with no clear standard treatment options.
- The combined targeted therapy and immunotherapy strategy has been widely used in advanced HCC.
- The specialized adjuvant therapy such as thymosin, bisphosphonates, antiviral medication, and vitamin C supplementation have been shown to somewhat potentiate the efficacy of target-immunity combination antitumor therapy and to reduce toxic side effects and the risk of recurrence and metastasis.

What is the implication, and what should change now?

- The combination regimen may enhance advanced huge HCC treatment and provide a new multimodal drug strategy for HCC.
- After the treatment with a multimodal combination regimen, patients with advanced large HCC have been downstaged. They may have the opportunity to undergo surgery or ablation to further treat the tumor.
- We need to conduct clinical trials to validate that the combination drug regimen has a better survival benefit for patients with advanced large HCC.

Case presentation

Medical history

A 58-year-old male patient presented to the Department of Oncology of The First Affiliated Hospital of Jinan University on December 31, 2020, with a 2-week history of right upper abdominal pain. A huge type of mass shadow was seen in the right lobe of the liver on abdominal computed tomography (CT). He had a 10-year history of HBV infection without taking antiviral medications regularly. He had a "cholecystectomy" over 10 years ago. The patient had a history of smoking for more than 20 years and had no drinking habits. His family history was unremarkable.

Physical examination

Physical examination revealed tightness of the right abdominal muscles, mild tenderness in the right upper abdomen, and a palpable hard liver 5 cm below the rib margins in the right midclavicular line. Murphy's sign was negative, and drumming sounds were heard on abdominal percussion.

Laboratory examinations

Laboratory tests showed that serum α-fetoprotein (AFP)

level was 436, 448 ng/mL. Child-Pugh liver function assessment score was 5, corresponding to class A. Eastern Cooperative Oncology Group performance status (ECOG-PS) score was 1. Serum HBV DNA was measured as 3.43E+002 IU/mL.

Imaging examinations

The patient underwent routine magnetic resonance imaging (MRI) scans, with the imaging outcomes depicted below (*Figure 1A-1E*). After first hospitalization, MRI of the epigastrium showed a large oval occupying space in the right lobe of the liver at S5/S6, measuring about 12.4 cm × 9.8 cm × 11.6 cm (*Figure 1A*); multiple round-like abnormal signals could be seen in the liver around the mass, with the larger one measuring about 2.0 cm × 1.5 cm × 1.1 cm. Chest CT showed numerous solid nodules in both lungs that were considered to be metastatic foci.

Final diagnosis

Based on these results, a diagnosis of huge HCC with multiple intrahepatic metastases (combined with distant lung metastases) was considered. This was diagnosed as Stage C according to the Barcelona Clinical Liver Cancer (BCLC) staging system and Stage IIIb according to the China Liver Cancer Staging criteria.

Treatment

Following evaluation of liver and kidney function, a combined targeted therapy and immunotherapy strategy was implemented, comprising apatinib 250 mg orally once daily, camrelizumab 160 mg every 21 days, and bevacizumab injection 400 mg. During the treatment period, tegafur 40 mg was administered 14 days on and 7 days off. Adjuvant treatment options included thymosin for immune enhancement, bisphosphonates for prevention of bone destruction due to tumor metastases, vitamin C supplementation, and a regular antiviral regimen with entecavir dispersible tablets 0.5 mg qd. After 12 months of combination therapy, we performed microwave ablation (MWA) on the patient and maintained the combination regimen for a long time after the procedure.

Outcome and follow-up

Imaging examination and monitoring of corresponding markers were performed regularly. Following two courses of treatment, MRI of the upper abdomen demonstrated a notable reduction in the size of the HCC in the right lobe of the liver, with a volume of approximately 5.6 cm × 4.8 cm × 5.6 cm (*Figure 1B*). Additionally, the original small intrahepatic metastases were not visible. Chest contrast-enhanced CT revealed a significant reduction in the size of the multiple solid nodular lesions in both lungs. Partial response (PR) was achieved according to the modified Response Evaluation Criteria in Solid Tumors (m-Recist) criteria. Serum HBV DNA was no longer detectable. After receiving eight cycles of combination therapy, the liver tumor lesions were significantly reduced (*Figures 1C,2*). Serum AFP level decreased to 73.61 ng/mL (*Figure 3*). Throughout the treatment period, the patients were regularly tested for hepatic function indices and blood changes, and no grade 3/4 adverse events (AEs) were observed. In December 2021, AFP was 468.94 ng/mL, which was higher than before. MRI showed a lesion of about 5.7 cm × 5.2 cm × 4.3 cm. After evaluation, the isolated lesion in segment S6 was stable, with a diameter >5 cm. The patient's general condition was good (ECOG-PS score 1, Child-Pugh class A liver function). Ultrasound-guided MWA of the liver mass was performed. The combination drug regimen of target-immunity plus adjuvant therapy was maintained postoperatively with regular follow-up. Until January 2022, a review of abdominal MRI showed that the size of the HCC lesion in the right lobe of the liver was reduced, with a size of about 5.0 cm × 4.8 cm × 4.9 cm, and no abnormal enhancement foci were seen locally (*Figure 1D*). AFP was reduced to normal value (17.26 ng/mL) (*Figure 3*). Until the last follow-up imaging assessment of the disease showed PR (*Figure 1E*). During this period, AFP levels fluctuated between 34.8 and 1,185.34 ng/mL, and liver function indices were maintained at normal (*Figure 4*). During the treatment period, no severe AEs of grade 3 or 4 were recorded. The patient experienced only mild anemia, with the lowest hemoglobin level being 106 g/L. Thrombocytopenia was observed, with the lowest platelet count at 101.9×10^9/L. The patient underwent therapy to enhance hematopoiesis and increase platelet levels, resulting in an improvement without significant discomfort.

This case showed successful comprehensive treatment of huge HCC. The patient with advanced BCLC Stage C HCC was treated with TKIs in combination with ICIs before and after MWA of the liver mass, supplemented with a combination of drug regimens. Tumor progression was

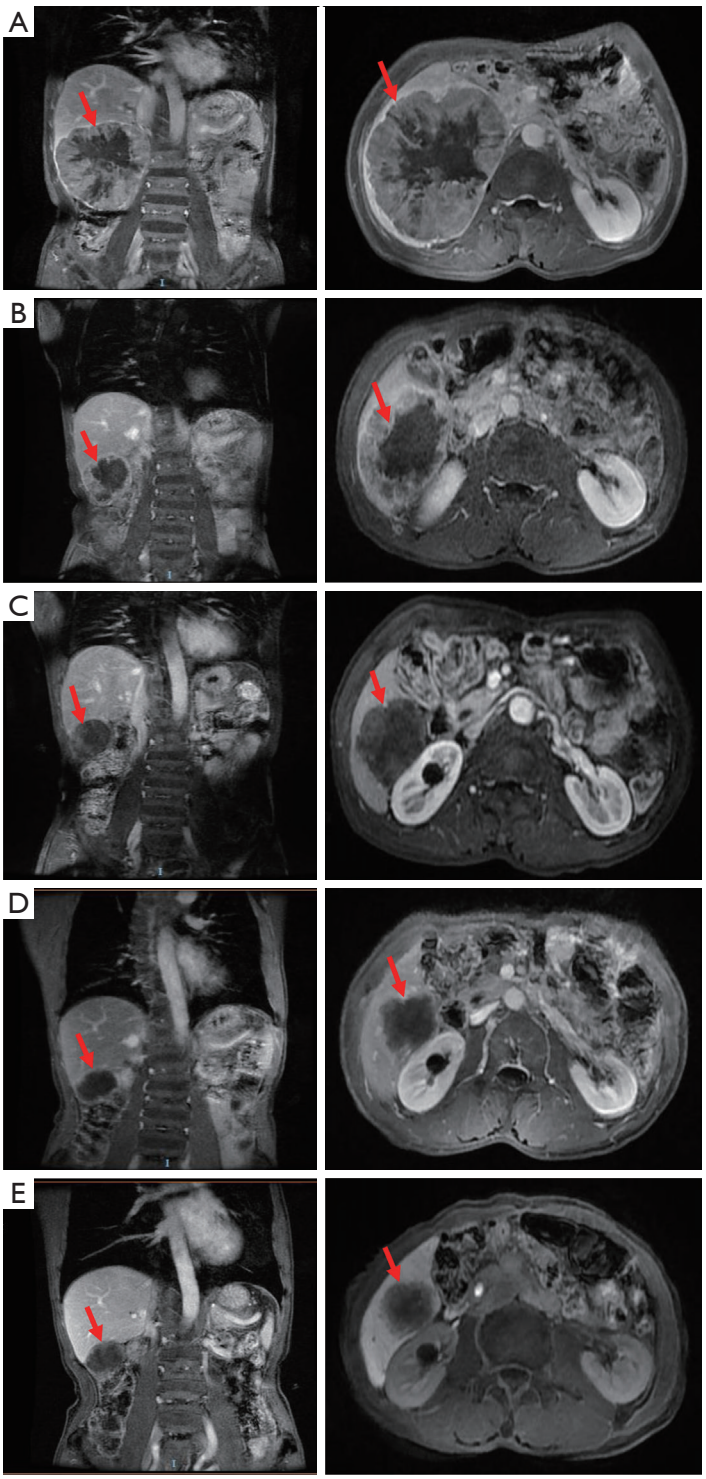

Figure 1 MRI scan image showing the progress of HCC. (A) Baseline condition of the tumor before treatment. Primary huge lesion of HCC (red arrows). (B) The tumor condition after two cycles of treatment. A notable reduction in the size of the HCC (red arrows). (C) The tumor condition after eight cycles of treatment. The tumor lesion has continued to decrease in size (red arrows) and has achieved PR. (D) Post-operative situation of MWA. The tumor focus was reduced in size compared to its previous dimensions (red arrows). (E) The last follow-up imaging assessment. The size of the tumor lesion in the right lobe of the liver has remained stable (red arrows). MRI, magnetic resonance imaging; HCC, hepatocellular carcinoma; PR, partial response; MWA, microwave ablation.

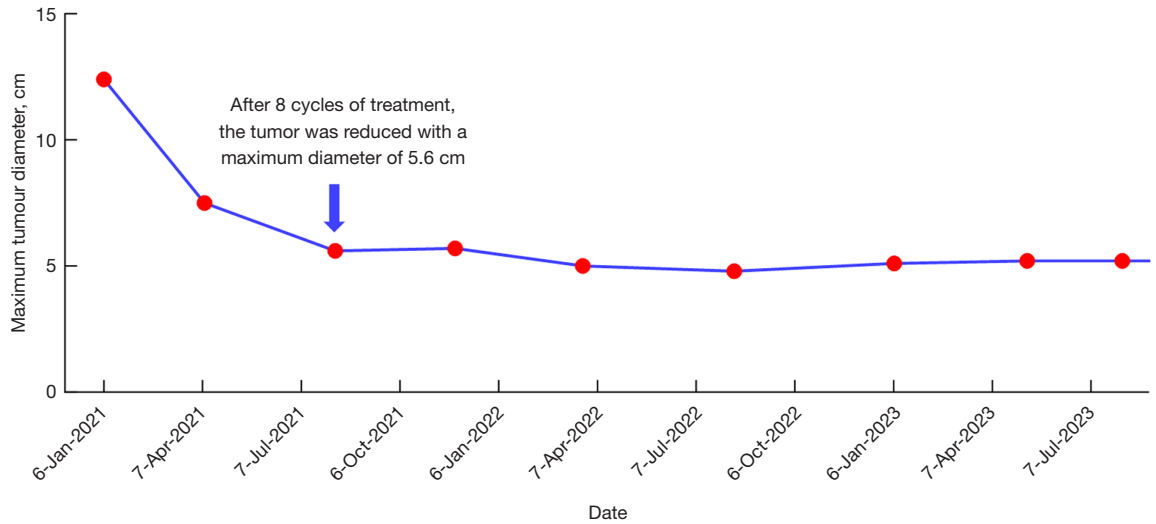

Figure 2 Alterations in maximum tumor diameter during treatment.

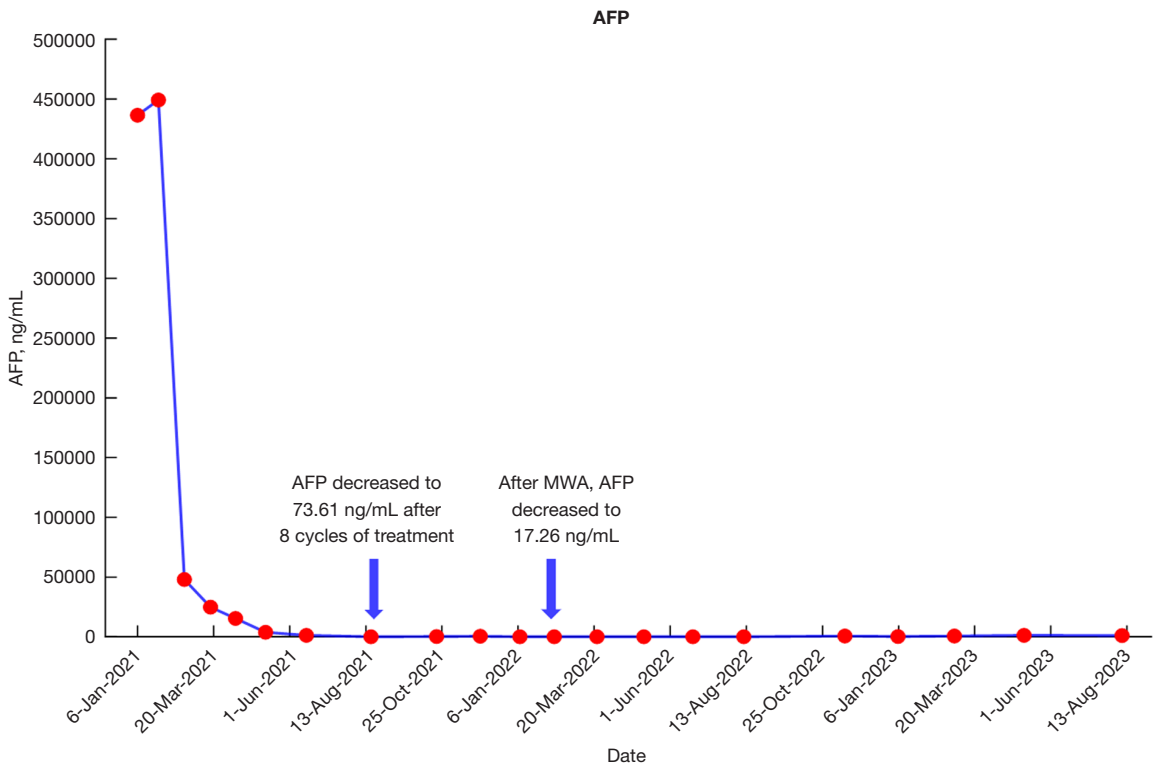

Figure 3 Alterations in serum AFP levels during treatment. AFP, α-fetoprotein; MWA, microwave ablation.

effectively controlled, resulting in a 58.1% reduction in the maximum diameter of the tumor and reduction in tumor load. The patient's complete treatment procedure is shown in *Figure 5*.

Ethical statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki

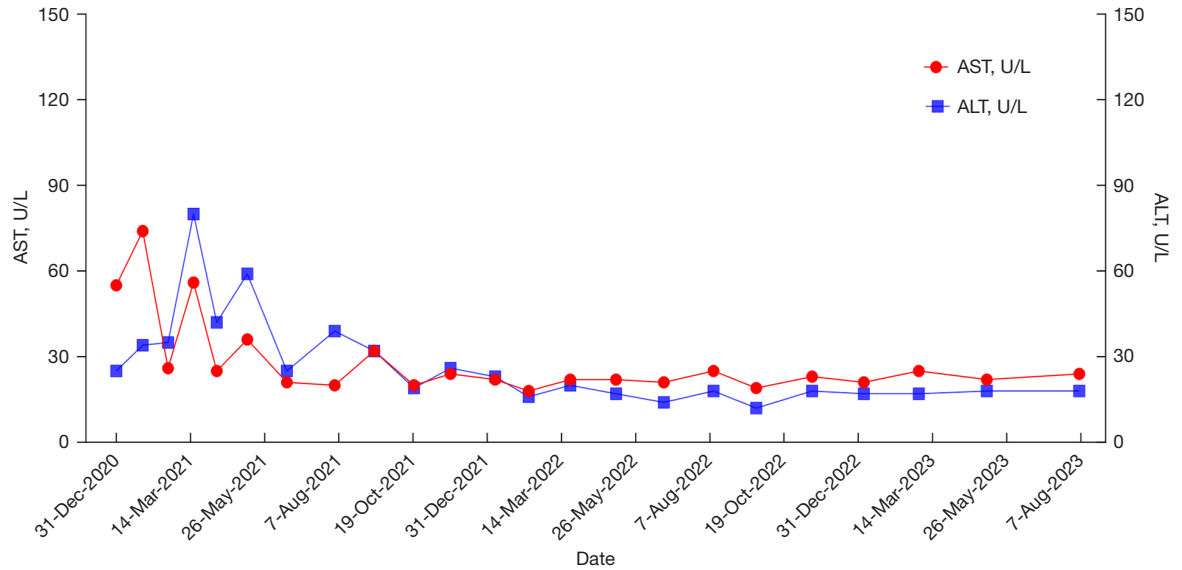

Figure 4 Alterations in AST/ALT level during treatment. AST, aspartate aminotransferase; ALT, alanine aminotransferase.

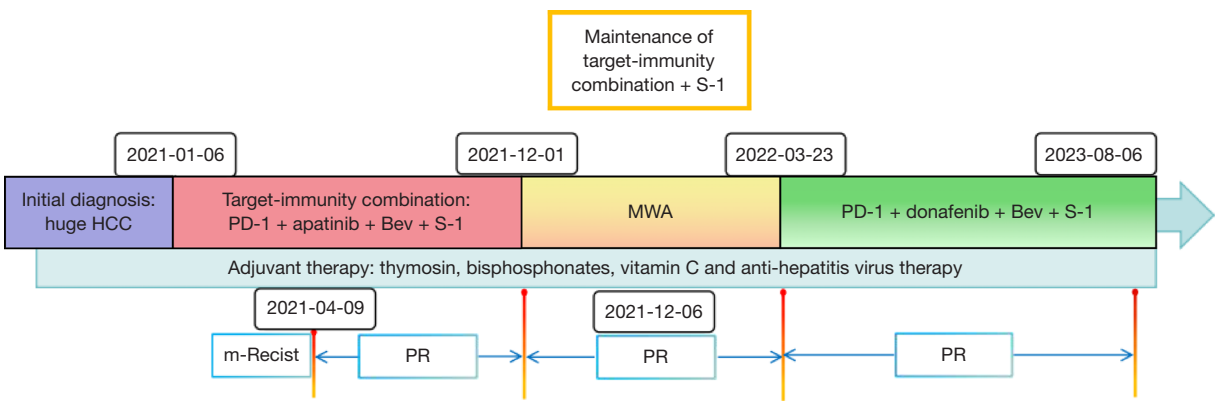

Figure 5 The complete treatment procedure. HCC, hepatocellular carcinoma; PD-1, programmed cell death protein-1; Bev, bevacizumab; S-1, tegafur; MWA, microwave ablation; m-Recist, modified Recist; Recist, Response Evaluation Criteria in Solid Tumors; PR, partial response.

Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

According to the treatment of huge HCC, there are case reports of feasible target-immunity combination therapy for tumor downstaging followed by liver transplantation or resection, achieving a good survival benefit (6). We tried a novel therapeutic approach that achieved positive results, adding multidimensional treatment to the combination of immunotherapy and targeted therapy. Our patient also achieved a long progression-free survival (PFS) time and realized the treatment's non-invasive and less adverse effects.

Developing targeted therapeutic and immunotherapeutic agents has brought new hope to patients with advanced HCC. Apatinib is a highly specific small molecule VEGFR-2 TKI that can prevent downstream signaling pathways and inhibit tumor angiogenesis. Apatinib can also regulate platelet-derived growth factor receptor α, insulin-like growth factor-1 receptor and serine/threonine protein kinase (AKT) phosphorylation levels, thereby disrupting

the PI3K/AKT signaling pathway and inducing HCC cell apoptosis. It also displays excellent immunoregulatory activity, inducing natural killer (NK) cell activation, elevating interferon-γ levels, and reducing tumor necrosis factor-α and interleukin-6 levels (7). Furthermore, research has revealed the potential of apatinib to overcome resistance in HCC, demonstrating its extensive therapeutic potential.

However, new therapeutic strategies are urgently needed as the survival benefit rate associated with TKIs remains low and adverse effects are high. The emergence of ICIs is seen as an important innovation in treating HCC and is expected to be a major cornerstone of systemic therapy for advanced HCC (8). Recently, many reports and clinical studies have indicated that combination therapies have shown promising results for the treatment of HCC (9). For example, the Himalayan trial demonstrated the superiority of durvalumab-tremelimumab (STRIDE regimen) over sorafenib, establishing a new first-line option for patients with advanced or unresectable HCC (10). Other examples are the IMbrave150 and ORIENT-32 studies, which recommended atezolizumab in combination with bevacizumab (AteBev regimen) and sintilimab in combination with bevacizumab biosimilar (IBI305) for the first-line treatment of patients with unresectable HCC, which significantly improved overall survival (OS) and PFS (11). Since bevacizumab is a single-target [vascular endothelial growth factor (VEGF)] inhibitor, the therapeutic efficacy may be further improved if ICIs are combined with multikinase inhibitors including apatinib, donafenib or lenvatinib.

Several studies have indicated that immunotherapy and targeted therapy can be used to enhance efficacy. Motz *et al.* showed that the blood supply of large HCC was abundant. The antiangiogenesis-targeted drug apatinib improved the hypoxic and immune microenvironment of tumors, while promoting tumor vascular normalization, reversed VEGF-mediated immunosuppression, and promoted T-cell infiltration in tumors, thus enhancing anti-programmed cell death protein-1 (PD-1) and anti-programmed cell death ligand 1 (PD-L1) effects (12). A multicenter study demonstrated that apatinib benefited patients with advanced HCC and lung metastases, with significantly prolonged median PFS and overall response (13). Therefore, for our patient with advanced huge HCC, we chose the treatment regimen of apatinib combined with camrelizumab, by this, the tumor can be treated with surgery or ablation after the tumor has been downstaged following the combination of drug treatments. The clinical benefits of the combination regimen of apatinib and camrelizumab have been reaffirmed by the recent RESCUE and SHR 1210-III-310 clinical studies conducted in China. The study showed that the combination of camrelizumab and apatinib in advanced HCC had significant clinical benefits and a tolerable safety profile (14). The 2022 edition of the Chinese Society of Clinical Oncology guidelines for the treatment of primary HCC has already included the combination of camrelizumab and apatinib regimen as a first-line treatment option for advanced HCC. Studies have shown that combination of targeted therapy and immunotherapy reduces the activity of the mitogen-activated protein kinase (MAPK) pathway and PI3K/AKT signaling pathways and restrains the immunosuppressive impact of tumor-associated regulatory T cells. It also boosts the number and function of killer immune cells like T cells and NK cells (15). These mechanisms have helped to explain the success of combination of targeted therapy and immunotherapy in treating HCC.

After combination regimen therapy, the tumor volume and serum AFP decreased significantly, and the solid nodular lesions in both lungs were significantly smaller and fewer than before. The tumor lesions remained stable with a size of 5.7 cm × 5.2 cm × 4.3 cm, so we planned to reduce the tumor load by surgical means. Currently, in the field of HCC treatment, surgical resection is used as the treatment of choice for adults with solitary lesions <5 cm in size (16). However, surgical resection of a single large (>5 cm) or huge (>10 cm) remains a challenge, with the possible risk of massive bleeding and postoperative fatal complications (17). Local ablative treatment offers a curative option for patients with small-sized HCC (usually <3–4 cm) that is inoperable, achieving a 3-year recurrence-free survival (RFS) rate of ~46% and an OS rate of ~76% (18). However, once the tumor size exceeds 3 cm, patients have lower objective response rate (ORR), higher recurrence rates, and poorer OS (19). MWA is a type of local ablation technique, which is mainly performed by applying high-frequency electromagnetic waves to human tumor tissues, leading to dehydration and charring death of tumor cells (20). Systematic reviews and meta-analyses have shown that MWA demonstrates superior overall local control rates compared to radiofrequency ablation (RFA) (21). A previous meta-analysis by Facciorusso *et al.* showed that MWA was significantly superior to RFA in controlling the rate of local recurrence in patients with high tumor load (tumor size >20 mm) (22). These results suggest that MWA may be a

superior option in the treatment of large HCC and holds promise as an effective alternative for the treatment of unresectable HCC. After comprehensive evaluation of the patient's condition, we performed MWA.

Combined targeted therapy and immunotherapy was the mainstay in our patient, and he had the opportunity to undergo surgery or ablation to further treat the tumor. In addition, the use of chemotherapeutic agents, antivirals, vitamins, and bisphosphonates in the combination regimen also played an important role. In our combination drug regimen, long-term regular oral chemotherapy with the 5-fluorouracil (5-FU) analog tegafur was also an important component. 5-FU is approved for first-line treatment of locally advanced and metastatic HCC that is not amenable to surgical resection or local treatment (23). Data from phase III trials have shown that folic acid, 5-FU and hepatic arterial infusion chemotherapy (FOLFOX) are superior to transcatheter arterial chemoembolization (TACE) in patients with large, unresectable intermediate-stage HCC (24). In another systematic review and meta-analysis, 5-FU was confirmed as a suitable drug choice in an HCC treatment strategy in combination with apatinib (25). Multiple lines of evidence suggest that the selection of the 5-FU analog tegafur for inclusion in combination regimens holds promise. However, chemoresistance to 5-FU is an issue for a variety of other cancers. HCC stem cells are thought to be responsible for the progression of chemoresistance and tumor growth (26). It has been found that vitamin C preferentially kills cancer stem cells (CSCs) in HCC via sodium-dependent vitamin C transporter-2 (SVCT-2). Therefore, as a drug to eradicate CSCs, vitamin C in combination with chemotherapeutic agents may be a promising strategy for the treatment of HCC (27).

In the present case, another major therapeutic feature was adjuvant therapy with thymosin combined with bisphosphonates. Thymosin α1 is a thymic hormone with antitumor and immune-enhancing effects, and it reduces the adverse effects of radiotherapy. Its synthetic form, thymosin, is approved for the treatment of hepatitis B and C in several countries (28) and has been used in patients with lung cancer, melanoma, breast cancer, and HCC to improve the immune environment and increase the tumor response rate, thereby improving patient survival rates (29). A retrospective study evaluated thymosin α1 as adjuvant therapy for patients with primary HBV-related HCC after hepatectomy and found that it improved liver function, OS and RFS (30). In summary, in treating patients with HBV-associated HCC, thymosin may serve various functions such as antiviral and antitumor activity, immune enhancement, and reduction of drug toxicity. Injectable disodium incadronate belongs to the third generation of bisphosphonates and is currently mainly used to reduce the pain of bone metastases. It mainly inhibits osteoclast activation by inhibiting bone mineralization or bone resorption, and at the same time, inhibits tumor cells from settling, proliferating and surviving in the bone matrix, and improves the bone microenvironment (31). Our previous studies have shown that zoledronic acid and thymosin α1 achieved good efficacy in the treatment of prostate cancer and reduces the risk of bone metastasis. We further conducted basic experimental studies and found that thymosin in combination with bisphosphonates can alter the tumor immune profile by modulating the MyD88/NF-κB pathway *in vivo*, promoting macrophage and T-cell activity, and sensitizing immunotherapy (32). Other studies have shown that zoledronic acid improves the local control of bone metastasis and prevents the growth of HCC primary and new metastatic lesions by terminating the valproic acid pathway, inhibiting the MAPK pathway and inducing apoptosis in HCC cells (33). Vitamin C is an antioxidant that is often depleted by oxygen free radicals released by advanced tumors. The use of vitamin C in tumor therapy is supported by evidence that it can kill tumor cells by inducing a peroxidative stress response and modulating hypoxia-inducible factor-1 activity. Vitamin C can also regulate epigenetic expression, reduce the malignancy of tumor cells, increase the sensitivity of antitumor drugs, and reduce chemotherapy-related toxicity in cancer patients (34). Recently, some studies have shown that vitamin C can induce vascular normalization in HCC, enhance lymphocyte recruitment and transendothelial migration, and improve the efficacy of immunotherapy by stimulating tumor TET2 and accelerating upregulation of the positive feedback loop of the cGAS/STING pathway (35). Therefore, vitamin C may be part of a potential synergistic regimen for immunotherapy and chemotherapy in HCC. However, there is still a lack of high-level clinical trial evidence supporting the use of vitamin C, and its specific anticancer efficacy and mechanism remain to be explored.

Therefore, we chose thymosin combined with bisphosphonate drugs to enhance the patient's immunity and improve anti-tumor efficacy. Thymosin combined with oral nucleoside (acid) analogue was used to combat hepatitis virus and prevent tumor recurrence. Vitamin C can reduce the side effects of drug therapy and fight against chemotherapy resistance. Bisphosphonates can reduce

the risk of tumor metastasis. This multimodal treatment model of drug regimens could improve the efficacy of antitumor therapy, providing better clinical benefit to the patients. Following MWA, we sustained the combination regimen. Research has indicated that age, the size of the primary tumor, tumor dimensions exceeding 5 cm prior to ablation, and elevated serum AFP levels before ablation are significant risk factors associated with the recurrence of HCC following MWA. The immune profiles of patients experiencing recurrence were characterized by the predominance of PD-1/PD-L1 tumor immunotherapy signaling pathway activation, whereas in those without recurrence, Th1 signaling pathway activation was more prevalent. This suggests that the likelihood of recurrence increases if the body's immune system is not reconstituted following ablation therapy (36). The combination regimen may aid in immune reconstitution for HCC patients, potentially lowering the recurrence rate. Our extended follow-up revealed that the patient's overall health, as well as liver, kidney, and bone marrow functions, remained in good condition. Alternative maintenance therapies could include targeted therapy in conjunction with immunotherapy, such as 1,200 mg atezolizumab plus 15 mg/kg bevacizumab every 3 weeks for 17 cycles (12 months) which can improve the RFS rate. The case report indicates that the combination regimen may potentially play a role in decreasing toxicity and enhancing efficacy.

Our patient maintained PR without disease progression for 20 months after MWA until August 2023.

Conclusions

Huge HCC often implies poor prognosis and therapeutic difficulty. In the era of combined targeted therapy and immunotherapy for advanced HCC, how to develop a multimodal dosing strategy to achieve better clinical outcomes and control lower adverse drug reactions is a clinical problem. Our case of BCLC Stage C huge HCC provides a basis for developing a comprehensive treatment strategy for advanced huge HCC. Meanwhile, we need to continue to explore how to improve the initial diagnosis rate of HCC, and the mechanism of synergistic combination therapy, and combine with multidisciplinary teams to explore new multimodal combination regimens.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tgh.amegroups.com/article/view/10.21037/tgh-24-91/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tgh.amegroups.com/article/view/10.21037/tgh-24-91/coif). The authors have 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. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

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