Complete pathological response with diabetic ketoacidosis to the combination of sintilimab and anlotinib in an unresectable hepatocellular carcinoma patient: a case report

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Most hepatocellular carcinoma (HCC) patients have dismal prognoses because they are already in the advanced stage at the time of initial diagnosis and are unable to undergo upfront surgery. Recent studies of immune checkpoint inhibitors (ICIs) and antiangiogenic agents (AAAs) have shown encouraging results for unresectable HCC (uHCC). Here, we report a patient with uHCC who was treated with a combination of anlotinib and sintilimab (sintilimab 200 mg, intravenous glucose tolerance test, q21d and anlotinib 12 mg, orally, d1–14, q21d), an analog of the combination of lenvatinib and pembrolizumab with much lower cost. The patient with recurrent uHCC was downstaged to resectable disease by the combination therapy. After eight cycles of treatment with anlotinib and sintilimab, the patient underwent a second operation. The histology of the resected mass revealed a major and almost complete pathological response. However, this patient was diagnosed with type I diabetes mellitus with ketoacidosis after nearly 10 cycles of combination treatment with anlotinib and sintilimab. Active follow-ups revealed no signs of local recurrence or distant failure. In conclusion, this case report demonstrated that the combination of anlotinib and sintilimab, one of the strategies combining ICIs with AAAs, showed promising efficacy in the treatment of uHCC patients. *Anti-Cancer Drugs* 33: e741–e746 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, accounting for approximately 700 000 deaths each year worldwide [1]. Surgery and liver transplantation are still the main curative treatments for HCC patients. However, at present, approximately 80% of HCC patients are already in the advanced stage at the time of initial diagnosis and do not meet the indications for upfront surgery. The prognosis of patients with unresectable HCC (uHCC) is dismal [2]. Systemic therapy may downstage and transform some advanced uHCC cases into resectable HCC. Neoadjuvant therapies may also reduce the tumor burden and increase the chance of R0 resection in selected patients. After successful resection of the tumor, HCC patients can achieve much better survival [2]. Therefore, various strategies have been explored to convert uHCC into resectable HCC by integrating systemic and local therapies.

For the past decade, sorafenib has been the first-line treatment for patients with uHCC [3]. Until recently, lenvatinib was shown to be noninferior to sorafenib in the first-line setting based on the results of the REFLECT study [4]. Lenvatinib is a multi-targeted tyrosine kinase inhibitor (TKI) antiangiogenic agent (AAA) targeting vascular endothelial growth factor receptors (VEGFR)1–VEGFR3, fibroblast growth factor receptors (FGFR)1–FGFR4, platelet-derived growth factor receptor-α (PDGFR-α), RET, and KIT [5,6]. Immune checkpoint inhibitors (ICIs) have emerged as a promising treatment strategy for HCC [7]. Two anti-programmed cell death-1 (PD-1) antibodies, nivolumab [8], and pembrolizumab [9] have been approved for the second-line treatment of HCC. However, only a minority of HCC patients could benefit from these monotherapies. Recently, strategies combining immunotherapy and molecular targeted therapy have been proposed for the development of curative therapies for cancers by reducing the tumor volume [10]. ICIs combined with AAAs (ICI+AAA) have emerged as a promising treatment for cancers [11], including HCC [12,13]. Among these ICI+AAA strategies, lenvatinib combined with pembrolizumab has demonstrated remarkable

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antitumor efficacy and tolerable toxicity in patients with uHCC [14,15].

Unfortunately, both lenvatinib and pembrolizumab are expensive and have not yet been universally covered by governmental health insurance in China. Hence, the combination therapy of lenvatinib and pembrolizumab is not available for the vast majority of Chinese cancer patients. Alternatively, the cost of drugs made domestically or made by joint ventures is much less expensive, which renders opportunities to benefit a large number of Chinese patients. Sintilimab (Tyvyt), developed by Innovent Biologics Company in collaboration with Eli Lilly China, is a fully human IgG4 mAb that binds to PD-1. It blocks the interaction of PD-1 with its ligands (PD-L1 and PL-L2) and consequently helps to restore the endogenous antitumor T cell response [16]. Anlotinib hydrochloride is a novel small molecule multi-targeted TKI that inhibits VEGFR, PDGFR, FGFR, c-Kit, and other kinases; it was codeveloped by Jiangsu Chia-Tai Tianqing Pharmaceutical (Lianyungang, Jiangsu, China) and Advenchen Laboratories (Moorpark, California, USA) [17,18]. Sintilimab and anlotinib share similar antitumor mechanisms with pembrolizumab and lenvatinib, respectively. Sintilimab combined with anlotinib has been shown to be highly effective and well tolerated in the first-line treatment of advanced non–small-cell lung cancer [19]. Therefore, we hypothesize that this combined therapy might mimic the antitumor efficacy and safety of lenvatinib combined with pembrolizumab in the treatment of Chinese patients with uHCC. Here, we report a patient with uHCC who obtained a major pathological response by the combination therapy of anlotinib and sintilimab.

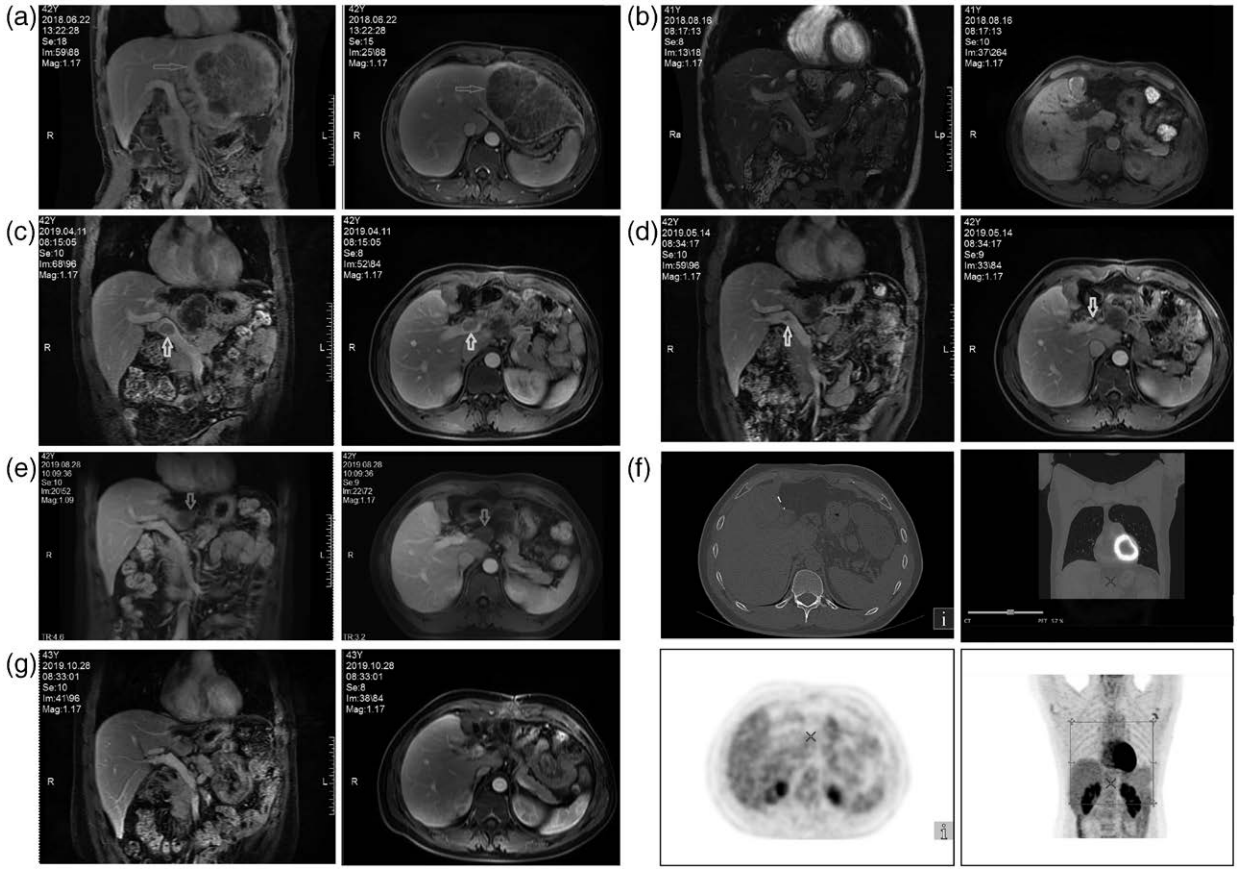
Case presentation

A 42-year-old Chinese man was admitted for abdominal pain and fever in June 2018. He had a long history of hepatitis B virus infection and regular antiviral medication for almost 20 years. An abdominal computed tomography (CT) scan suggested a large mass ($9.2 \times 12.3 \times 12.5\,cm^3$) with heterogeneous enhancement in the left lobe of his liver (Fig. 1a). The mass occupied the entire left lobe with enlarged hepatic hilar lymph nodes. His serum α-fetoprotein (AFP) was 42.6 ng/mL (normal range: 0–8.1 ng/mL), and his liver function was Child-Pugh class A (total bilirubin: 11.8 μmol/L; albumin: 38.6 g/L; no hepatic encephalopathy, no ascites, and normal clotting time). The patient underwent R0 left liver lobectomy and cholecystectomy on 27 June 2018. There were also no remaining lesions on MRI at the first follow-up examination on 16 August 2018, after the operation (Fig. 1b). His serum AFP levels became normal at 2.6 ng/mL. The pathology after surgery showed poorly differentiated HCC with no cancer cells in the gall bladder (Fig. 2a and b). Immunohistochemistry showed negative AFP, Arg-1, glypican-3, and hepatocytes and positive CK7, CD34 (capillary type), and Ki67 (Li 70%). Subsequently, the patient underwent transarterial embolization of the primary lesion area in the left liver lobe in August 2018. The patient's serum AFP levels remained normal, and liver function tests were also normal in the regular bimonthly follow-up until he was hospitalized again for abdominal pain and fatigue in April 2019. By this time, his AFP was 2.5 ng/mL. Both abdominal MRI and CT showed a liver hilar nodular mass of 4.6 cm in greatest dimension, together with a tumor embolism in the main branch of the portal vein (PVTT, $1.7 \times 1.5\,cm^2$) on 11 April 2019 (Fig. 1c).

After multidisciplinary tumor board (MDT) discussion, the lesion was considered unresectable at that time, and transformative systematic treatment was suggested. After fully informed consent was obtained, the patient refused chemotherapy and monotherapy by either sorafenib or lenvatinib and decided to receive immunotherapy combined with antiangiogenic therapy (sintilimab 200 mg, intravenous glucose tolerance test, q21d and anlotinib 12 mg,orally, d1–14, q21d) on 18 April 2019. After 1 month of treatment, the AFP and carcinoembryonic antigen levels remained normal. Both the size of the hepatic hilar nodule ($3.2 \times 3.7\,cm^2$) and thrombus ($0.9 \times 1.1\,cm^2$) were reduced in abdominal MRI examination on 14 May 2019 (Fig. 1d). Repeated laboratory tests before and after every cycle and thorough radiological examination every two cycles were performed. During the next 3 months, the patient underwent the third to seventh cycles of treatment. Follow-up MRI and CT scans on 15 July and 28 August (Fig. 1e) showed continuous shrinkage of both the hepatic hilar nodules ($2.9 \times 2.6\,cm^2$ on 15 July and $2.1 \times 1.8\,cm^2$ on 28 August) and PVTT ($0.5 \times 1.0\,cm^2$ on 15 July and not detected on 28 August). On 30 August 2019, PET/CT was performed and showed no significant standardized uptake value uptake in either the liver or other regions (Fig. 1f). Throughout the treatment cycles, the patient tolerated the treatment well, and no serious treatment-related toxicity was observed.

In the second MDT discussion on 30 August 2019, the patient's liver function remained Child-Pugh class A (total bilirubin: 8.2 μmol/L; albumin: 43.2 g/L; no hepatic encephalopathy, no ascites, and normal clotting time), and the lesion was deemed resectable at the moment. On 26 September after the eighth cycle of sintilimab 200 mg monotherapy and a month of stopping anotinib, the patient underwent the second operation. During the surgery, a $3 \times 3\,cm^2$ hard mass in front of segment I of the liver was found and resected. The pathology of the resected lesion indicated massive necrotic liver tissue ($3 \times 2.5 \times 2\,cm^3$) with sporadic dysplastic HCC cells, in which more than 95% of the tumor cells showed necrosis (Fig. 2c and d). Immunohistochemistry showed negative AFP and glypican-3 and positive CK7, CD34, and Ki67 (30%). The latest abdominal MRI on 28 October 2019 showed no mass or lesions (Fig. 1g). Subsequently, the patient was in active follow-up, which was largely eventless until November

Fig. 1



MRI scans and PET images showing the course of hepatocellular carcinoma in the liver. (a) The baseline tumor condition before surgery. (b) The liver condition after lobectomy. (c) The first progressive disease during follow-up. (d) Partial remission during the second cycle of sunitinib and anlotinib therapy. (e) The tumor condition before the second surgery after the seventh cycle of sunitinib and anlotinib therapy. (f) The corresponding PET images, with no significant SUV uptake in either the liver or other regions (SUVmax: residual liver tumor tissue=1.9; liver=2.9; mediastinal great vessels=1.9). (g) No residual tumor after re-surgery. SUV, standardized uptake value.

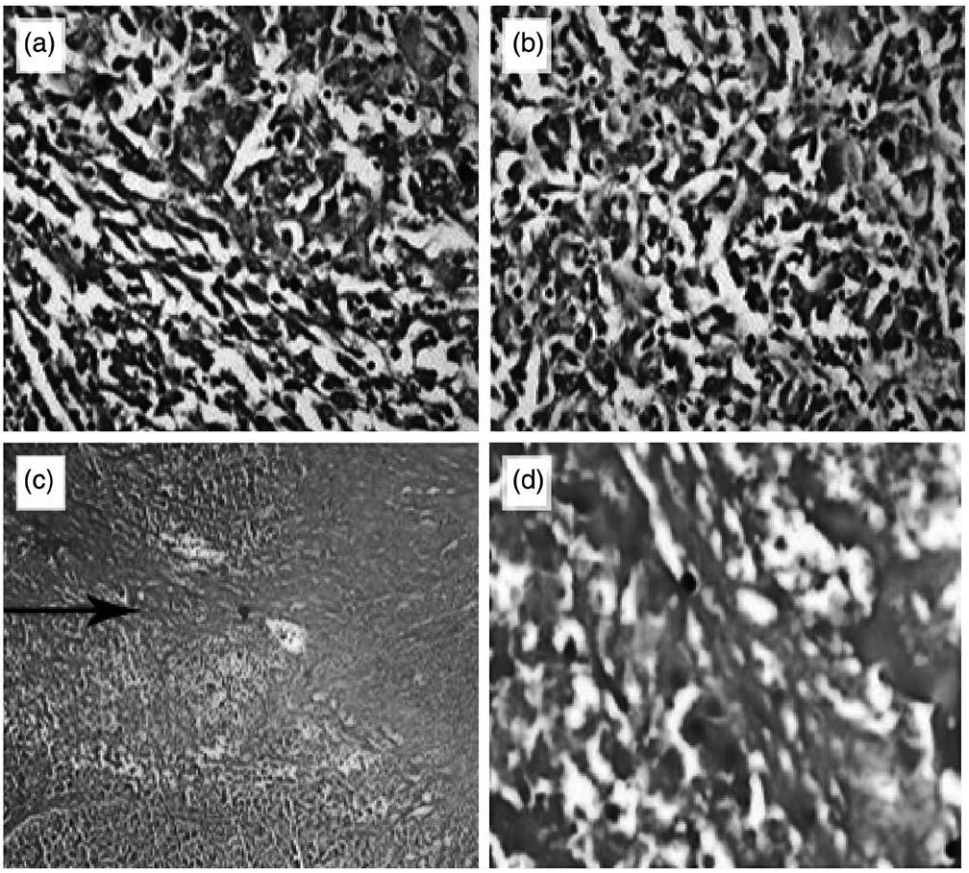
2019. Shortly before the 11th cycle of treatment, the patient complained of nausea, vomiting, thirst, and polyuria and was found to have ketoacidosis on urine analysis (urine ketone body +++) on 18 November 2019. The treatment of anlotinib and sintilimab was immediately discontinued. Although he had no history of diabetes mellitus and his blood sugar had been normal before, he was quickly tested for blood sugar levels. A fasting blood sugar level of 17.0 mmol/L was found, so he was subsequently tested for C-peptide and it was found that insulin secretion was almost zero. Tests for insulin and pancreatic antibodies (GA-DA, IA-2A, IAA, and ICA) were all negative. An endocrinologist was consulted, and a diagnosis of type I diabetes mellitus with ketoacidosis (DKA) was determined. The patient is now on diligent blood glucose monitoring and insulin supplementation treatment. Repeated follow-up examinations showed that he had been cancer free ever since the second resection, and his blood glucose levels were well controlled. The patient continues to use daily multiple insulin injections (basal glargine, 3–4 U/day; prandial insulin aspart, 3–4 U/meal). His last follow-up was on 25 May 2020. Over the whole period, his hemoglobin A1c levels were all within the normal range.

Discussion

To the best of our knowledge, this is the first reported case of a patient with HCC who underwent combined anlotinib and sintilimab treatment, an analog of a combination of lenvatinib and pembrolizumab. The combination therapy converted advanced uHCC into operable HCC, and a major and almost complete pathological response was observed after downgrading treatment. In line with the most recent results from the phase III trial of IMbrave150 [20], these promising results highlighted the remarkable efficacy of ICI+AAA in the treatment of uHCC.

At present, the first-line options for uHCC include sorafenib/lenvatinib and systemic chemotherapy. In uHCC patients with sorafenib treatment failure, regorafenib, cabozantinib, and ramucirumab are currently

Fig. 2



Pathological features of the tumor lesion after lobectomy and re-surgery. (a and b) Poorly differentiated hepatocellular cell carcinoma with massive necrotic liver tissue after lobectomy (original magnification x400). (c) Massive necrotic liver tissue with peripheral fibrous hyperplasia (original magnification x100). (d) Little dysplastic HCC in which more than 90% of tumor cells show necrosis after re-surgery (original magnification x400). HCC, hepatocellular carcinoma.

recommended [21]. However, the median overall survival (OS) of sorafenib was 10.7 months in the SHARP study [3] and 12.3 months in the REFLECT study [4]. Although the objective response rate (ORR) of lenvatinib was 40.6%, which was significantly higher than 12.4% for sorafenib, the median OS of lenvatinib was still only 13.6 months in the REFLECT study [7]. Encouragingly, the treatment for uHCC has now been entering into a new era of immunotherapy [7]. On the basis of the results of the CheckMate-040 study [8] and the KEYNOTE-224 study [9], the US Food and Drug Administration (FDA) has conditionally approved nivolumab and pembrolizumab for the second-line treatment of advanced HCC. In the MDT conference for this patient on 18 April 2019, the team discussed the encouraging results of Keynote-524, the phase Ib study of lenvatinib in combination with pembrolizumab, which had just been announced in the 2019 American Association for Cancer Research annual meeting [14]. This combination showed an ORR of 44.8% and a disease control rate as high as 93.3%. A consensus was reached that lenvatinib in combination with pembrolizumab should be attempted for this upfront unresectable but potentially transformable HCC case. Then, the encouraging results of Keynote-524 were discussed with the patient. Since lenvatinib is not yet available in mainland China and pembrolizumab is too expensive, the alternatives as well as the risks and benefits were also discussed in detail with the patient and his family. After fully informed consent, the patient decided to take the off-label combination treatment of anlotinib and sintilimab, the analog of the combination of lenvatinib and pembrolizumab, on 18 April 2019. Later during the treatment, this combination therapy received breakthrough therapy designation from the US FDA [22].

Moreover, the latest IMbrave150 results further broke the bottleneck of the first-line treatment of uHCC patients [20]. Treatment with the combination of atezolizumab, a PD-L1 inhibitor, and bevacizumab, a mAb targeting VEGF, resulted in significantly longer overall

and progression-free survival as well as strikingly better patient-reported outcomes than sorafenib. It is also the first positive randomized, phase 3 trial in defining the new role of atezolizumab–bevacizumab (i.e. ICI+AAA) in the expanding treatment landscape for uHCC. It is expected that atezolizumab combined with bevacizumab will be the new first-line treatment for uHCC [21].

Various conversion strategies have been attempted to downstage the disease with the aim of transforming uHCC into resectable HCC. The liver is an organ with high vascularization and immunogenicity. Laboratory results have shown that VEGF and other angiogenic factors induce abnormal blood vessel formation, which leads to hypoxia in the tumor microenvironment and difficulty of T cell aggregation around the tumor [11]. Hypoxia can suppress the function of various immune cells and activate the activity of myeloid-derived suppressor cells and regulatory T cells. The deterioration of the tumor microenvironment provides favorable conditions for tumor development and the suppression of immune function. VEGF or VEGFR inhibitors induce vascular normalization and thus reduce hypoxia, increase intratumoral infiltration and the survival of cytotoxic T lymphocytes, and decrease regulatory T lymphocyte recruitment, resulting in a more favorable immune microenvironment to enhance ICI antitumoral activity [23]. In HCC mouse models [24], this synergistic effect was specifically found for the combination of lenvatinib with anti-PD-1 mAb [13]. Therefore, a growing body of both preclinical and clinical evidence suggests that vascular normalization and immune reprogramming operate synergistically, resulting in the enhanced therapeutic efficacy of both ICIs and AAAs [23].

However, this remarkable antitumor efficacy may come with a cost: the risk of added toxicity [25]. This toxicity is sometimes fatal [26]. ICIs have been reported to cause immune-related adverse events (irAEs) [27], which can be a sign of benefit and durable response as well [28,29]. The causal relationship between sintilimab and the development of autoimmune diabetes is plausible since endocrine disorders are common irAEs caused by ICI treatment [28,30], and no evidence suggests that autoimmune diabetes is caused by antiangiogenic TKIs in this combination therapy [25]. ICI-induced diabetes may be due to cell-mediated immune activation [31]. Pancreatic islet beta-cell destruction is severe for most patients presenting with DKA and undetectable C-peptide, and ICI-induced irAEs is supposed to be irreversible [31]. However, there are no biomarkers to predict its onset, so regular screening for early detection is mandatory. The discontinuation of these agents following the best response and close follow-up until progression may be a treatment choice. This case also highlights the importance of an MDT in improving the treatment efficacy of HCC. At present, approximately 80% of HCC patients do not meet the indications for upfront surgery. Multidisciplinary collaboration in diagnosis and treatment integrates professional efforts from relevant disciplines and is critically important to make individualized, precise, evidence-based clinical decisions.

Conclusion

In summary, this preliminary study demonstrated the promising efficacy and safety of combining anlotinib and sintilimab, an example of the ICI+AAA strategy. Although we expect the further success of combined immunotherapy, the careful implementation of this strategy must be weighed against the added toxicity and be based on high-level evidence before it can be widely promoted. With the advancement of systemic therapy, there will be more strategies for transformative and neoadjuvant treatment. How to optimally select and apply these strategies to improve the survival of uHCC patients will certainly be the focus of future research.

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All datasets generated for this study are included in the article.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflicts of interest

There is no conflicts of interest.

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