Effects of Atezolizumab and Bevacizumab on Adrenal Gland Metastasis of Hepatocellular Carcinoma: A Case Report and Review of Literature

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Abstract:
Regarding the prognosis of cases with advanced-stage hepatocellular carcinoma (HCC), a recent clinical study showed that the immune checkpoint inhibitors atezolizumab plus bevacizumab have superior efficacy to sorafenib. However, only a few reports have focused on their effects on extrahepatic metastases. We herein report a case of HCC in a 59-year-old man with intrahepatic lesions treated successfully by hepatic arterial chemoembolization, radiotherapy, and sorafenib; the extrahepatic lesion in the adrenal gland was treated by atezolizumab plus bevacizumab. The patient showed a tumor-free condition for one year. We have summarized the clinical course and reviewed the literature to underscore the efficacy of atezolizumab plus bevacizumab for treating extrahepatic lesions of HCC.

Key words: hepatocellular carcinoma, metastasis, adrenal gland, atezolizumab plus bevacizumab

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver tumor with a high mortality rate and low five-year survival rate because of recurrence and metastases (1-3). The efficacy of the immune checkpoint inhibitors (ICIs) atezolizumab plus bevacizumab in improving the prognosis of advanced-stage HCC has been reported among various systemic chemotherapies (4, 5). However, only a few reports on the effects of this therapy on extrahepatic metastases have been published.

We herein report a case of HCC in a 59-year-old man with intrahepatic lesions successfully treated with hepatic arterial chemoembolization, radiotherapy, and sorafenib; the extrahepatic lesion in the adrenal gland was treated with atezolizumab plus bevacizumab.

Case Report

A 59-year-old man, 164 cm tall and weighing 79 kg, with alcoholic liver cirrhosis was referred to our hospital with a single 35-mm HCC in the anterior segment of the liver near the diaphragm. He had consumed approximately 100 mg alcohol per day for approximately 40 years and was a smoker with a Brinkman index of 555. Furthermore, he had a history of hepatic encephalopathy as well as alcoholic liver cirrhosis and splenic venous thrombosis treated with edoxaban tosilate hydrate. He was not suitable for surgery due to a poor hepatic reserve and radiofrequency ablation due to the tumor’s location, so transcatheter arterial chemoembolization (TACE) was done, followed by radiotherapy (50 Gy/25 Fr), which resulted in a complete response (Figure).

Small intrahepatic metastases were diagnosed a year after the therapy, so he underwent TACE seven times within two...
years. However, the tumor markers alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) increased after the seventh TACE procedure; therefore, TACE was considered unsuitable. Sorafenib (SOR) was then initiated at 400 mg orally as systematic chemotherapy, which resulted in a decrease in tumor markers and the disappearance of subtle intrahepatic metastatic lesions.

After maintaining stable disease for a year under the SOR treatment, the AFP and DCP levels increased from 3,479 ng/mL to 7,165 ng/mL and from 276.5 ng/mL to 541.5 ng/mL (Table 1), and computed tomography (CT) showed significant enlargement of the metastatic lesion in the left adrenal gland, with no liver tumors. Furthermore, laboratory data showed mild increases in transaminases, 7S domain of type IV collagen, autotaxin, and Mac-2 binding protein glycosylation isomer. In addition, serum lipid parameters and blood sugar levels were within normal ranges, and data for viral hepatitis markers were negative (Table 1).

The administration of edoxaban tosilate hydrate resulted in a reduced prothrombin time (%). The albumin-bilirubin (ALBI) score showed a tendency to recover upon abstinence from drinking and a reduction in TACE frequency. The patient declined surgical removal or additional radiotherapy for the metastatic tumor in the left adrenal gland; therefore, he was treated with a combination of atezolizumab and bevacizumab (ATZ+BEV) with pharmaceutical approval. The tumor markers AFP and DCP decreased to 19 ng/mL and 39.3 ng/mL, respectively, after three courses of ATZ+BEV ther-

Figure. A: Time-dependent changes in computed tomography (CT) images before the therapy (CT1); after the seventh TACE and Rx (CT2); four months after the SOR administration (CT3); one year after the SOR treatment (CT4); and after four courses of combination atezolizumab and bevacizumab (ATZ+BEV) (CT5). The images show the main tumor in the liver, intrahepatic metastases, and left adrenal gland. The red arrow shows the tumor in the liver, the red arrowheads show the intrahepatic metastases, and the white arrows point to the left adrenal gland. B: Clinical course. C: Time-dependent changes in albumin–bilirubin (ALBI) scores. Rx: radiotherapy
apy (Table 2), and CT showed remarkable shrinkage of the adrenal metastatic lesion. No adverse events were seen with the treatment and the liver function (represented by the ALBI score) remained stable; therefore, the treatment was continued (Figure). No tumor recurrence was noted for a year, so he was considered to have had a complete response to the therapies.

Table 1. Results of Laboratory Investigation before ATZ+BEV.

| Hematology | Biochemistry |
|------------|--------------|
| WBC 5,730 /μL | TP 7.3 g/dL |
| RBC 388×10⁴ /μL | Alb 3.6 g/dL |
| Hb 10.1 g/dL | BUN 21 mg/dL |
| PLT 31.6×10⁴ /μL | Cre 0.97 mg/dL |
| Coagulation | AST 41 IU/L |
| PT 36 % | ALT 35 IU/L |
| APTT 41.8 s | LDH 265 IU/L |
| Tumor Markers | γGTP 69 IU/L |
| AFP 7,165 ng/mL | CRP 0.21 mg/dL |
| AFP-L3 59.8 % | ACTH 19 pg/mL |
| DCP 541.5 ng/mL | Cortisol 8.2 μg/dL |
| NH3 123 μg/dL |  |

ATZ: atezolizumab, BEV: bevacizumab, WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, PLT: platelet, PT: prothrombin time, APTT: activated partial thromboplastin time, AFP: alpha-fetoprotein, AFP-L3: lectin-reactive alpha-fetoprotein, DCP: des-gamma-carboxy prothrombin, TP: total protein, Alb: albumin, BUN: blood urea nitrogen, Cre: creatinine, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γGTP: gamma-glutamyl transpeptidase, CRP: C-reactive protein, ACTH: adrenocorticotropic hormone, NH3: ammonia, TG: triglyceride, T-Cho: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, Col-IV-7S: 7S domain of type IV collagen, Fib4 index: fibrosis 4 index, ATX: autotaxin, M2BPGi: Mac-2 binding protein glycosylation isomer, HBs Ag: hepatitis B surface antigen, Anti-HBs: antibody for hepatitis B surface antigen, Anti-HCV: antibody for hepatitis C virus, HbA1c: hemoglobin A1c, FBS: fasting blood sugar

Table 2. Results of Laboratory Investigation after ATZ+BEV.

| Hematology | Biochemistry |
|------------|--------------|
| WBC 5,920 /μL | TP 7.2 g/dL |
| RBC 407×10⁴ /μL | Alb 3.5 g/dL |
| Hb 10.1 g/dL | BUN 20 mg/dL |
| PLT 31.6×10⁴ /μL | Cre 0.92 mg/dL |
| Coagulation | AST 33 IU/L |
| PT 33 % | ALT 22 IU/L |
| APTT 45.0 s | LDH 187 IU/L |
| Tumor Markers | γGTP 53 IU/L |
| AFP 19 ng/mL | CRP 0.11 mg/dL |
| AFP-L3 59.8 % | ACTH 27.4 pg/mL |
| DCP 354.5 ng/mL | Cortisol 6.8 μg/dL |
| NH3 123 μg/dL |  |

ATZ: atezolizumab, BEV: bevacizumab, WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, PLT: platelet, PT: prothrombin time, APTT: activated partial thromboplastin time, AFP: alpha-fetoprotein, AFP-L3: lectin-reactive alpha-fetoprotein, DCP: des-gamma-carboxy prothrombin, TP: total protein, Alb: albumin, BUN: blood urea nitrogen, Cre: creatinine, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γGTP: gamma-glutamyl transpeptidase, CRP: C-reactive protein, ACTH: adrenocorticotropic hormone, NH3: ammonia, TG: triglyceride, T-Cho: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, Col-IV-7S: 7S domain of type IV collagen, Fib4 index: fibrosis 4 index, ATX: autotaxin, M2BPGi: Mac-2 binding protein glycosylation isomer
HCC is the leading primary liver tumor with a high mortality rate and low five-year survival rate due to recurrence and metastases (1-3). Under these conditions, novel therapeutic strategies for systemic chemotherapy, including the multiple-kinase inhibitors of SOR, LEN, regorafenib, cabozantinib, and ICIs, have shown promising results (4, 5).

The efficacy of ICIs for lung cancer and malignant melanoma has been confirmed, which led to the investigation of ICIs’ efficacy against HCC as well. The IMbrave150 trial, which was published in 2020, showed that ATZ+BEV resulted in better overall and progression-free survival outcomes than SOR (5). In that study, the overall survival rate at 12 months was 67.2% in the ATZ+BEV group and 54.6% in the sorafenib group, while the median progression-free survival was 6.8 and 4.3 months, respectively. Aside from the occurrence of grade 3 or 4 hypertension in 15.2% of the cases, ATZ+BEV showed no high-grade toxicity, such as liver dysfunction. Since then, ATZ+BEV has become the first-line systemic treatment for advanced HCC (5).

As the 5-year survival rate of patients with extrahepatic metastasis was reported to be 8.0% (6), the presence of extrhepatic metastasis is a major factor determining the prognosis; therefore, the treatment of extrahepatic metastases of HCC can confer a prognostic and survival benefit (7). The prevalence of extrahepatic metastasis of HCC was reported to be 9.7% to 20% among all cases (8), with the lungs being the most common metastasis site (33.3%, 364 out of 1,094 cases had extrhepatic metastases), followed by the lymph nodes (30.7%, 336 in 1,094), bones (19.7%, 215 in 1,094), and adrenal glands (6.4%, 70 in 1,094) (6, 9).

While the IMbrave150 study showed that 63% of patients treated with ATZ+BEV had extrhepatic metastases, there have been only a few reports focusing on the therapeutic effects of ATZ+BEV on metastatic lesions. Table 3 summarizes the cases in which combination therapy showed a significant effect on extrhepatic metastases compared with other prior treatments (10, 11). No report has provided evidence on the timing of ATZ+BEV therapy suspension. Some reports have demonstrated the advantages of surgical removal of extrhepatic lesions provided intrahepatic lesions can be brought under control and the hepatic reserve function is maintained (9, 12). The further accumulation of clinical data should be done to demonstrate the advantages of ATZ+BEV treatment for extrhepatic metastases of HCC and to determine the suspension period of the treatment when a complete response is achieved.

In conclusion, the present case demonstrated the favorable effects of ATZ+BEV on extrhepatic metastases in the adrenal glands with few adverse events following the control of intrahepatic lesions by TACE, radiotherapy, and multi-kinase inhibitors.

The patient provided his written informed consent for the publication of this case report and any accompanying images.

The authors state that they have no Conflict of Interest (COI).

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