Table 1
The virological status of HBV of the patient and his family.

	Reference range	Patient			Sister	Mother
		Pre-chemotherapy	At the point of reactivation	At the time of entecavir start		
HBsAg	<0.05 IU/ml	<0.01	0.03	0.04	<0.01	9391.94
HBsAb	<10.00	405.00	0.74	3.8	23.47	0.37
HBcAb	<1.00 S/CO	0.05	0.05	0.1	0.08	10.58
HBeAg	<1.00 S/CO	NA	0.274	0.266	NA	0.254
HBeAb	<50%	NA	11.5	0	NA	99.7
HBV-DNA	<21.9 IU/mL (not detectable)	not detectable	<21.9 (detectable)	549.5	not detectable	8709.6

HBsAg: hepatitis B surface antigen, HBsAb: hepatitis B surface antibody, HBcAb: hepatitis B core antibody, HBeAg: hepatits B envelope antigen, HBeAb: hepatitis B envelope antibody, S/CO: signal to cut-off, NA: not available.

cantly decrease after chemotherapy in hematological malignancies [12]. Hence, the present case indicates that HBV reactivation with HBcAb-negative OBI occurs due to the disappearance of HBsAb as a result of PBSCT-related chemotherapy and immunosuppression treatment.

Considering the insights obtained in the present case, we conclude that HBV reactivation should be considered even in patients who have received HBV vaccination during infancy as protection against HBV infection transmitted from their mothers, especially for those under immunosuppressive conditions, such as allo-PBSCT.

Conflict of interest
None declared.

Acknowledgement

The authors would like to thank Professor Naoya Sakamoto (Hokkaido University Graduate School of Medicine, Japan) for critical reading.

References

[1] Choi J, Lim YS. Characteristics, prevention, and management of hepatitis B virus (HBV) reactivation in HBV-infected patients who require immunosuppressive therapy. J Infect Dis 2017;216(Suppl. (8):S778–84.
[2] Sugiyama M, Inui A, Shin-I T, Komatsu H, Mukaide M, Masaki N, et al. Easy-to-use phylogenetic analysis system for hepatitis B virus infection. Hepatol Res 2011;41:936–45.
[3] Mizokami M, Orito E, Ohba K, Ikeo K, Lau JY, Gojobori T. Constrained evolution with respect to gene overlap of hepatitis B virus. J Mol Evol 1997;44(Suppl. (1):S83–90.
[4] Pallier C, Castéra L, Soulier A, Hézode C, Nordmann P, Dhumeaux D, et al. Dynamics of hepatitis B virus resistance to lamivudine. J Virol 2006;80:643–53.
[5] Gonzalez SA, Perrillo RP. Hepatitis B virus reactivation in the setting of cancer chemotherapy and other immunosuppressive drug therapy. Clin Infect Dis 2016;62(Suppl. (4)):S306–313.
[6] Hoofnagle JH. Reactivation of hepatitis B. Hepatology 2009;49:S156–165.
[7] Yokoyama K, Kumagai H, Takahashi M, Nagashima S, Okamoto H, Yamagata T. Occult hepatitis B virus infection in immunized children born to carrier mothers. Pediatr Int 2017;59:1010–6.
[8] Wen WH, Chang MH, Zhao LL, Ni YH, Hsu HY, Wu JF, et al. Mother-to-infant transmission of hepatitis B virus infection: significance of maternal viral load and strategies for intervention. J Hepatol 2013;59:24–30.
[9] Stevens CE, Beasley RP, Tsui J, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. N Engl J Med 1975;292:771–4.
[10] Chen HL, Lin LH, Hu FC, Lee JT, Lin WT, Yang YJ, et al. Effects of maternal screening and universal immunization to prevent mother-to-infant transmission of HBV. Gastroenterology 2012;142:773–81.
[11] Paul S, Dickstein A, Saxena A, Terrin N, Viveiros K, Balk EM, et al. Role of surface antibody in hepatitis B reactivation in patients with resolved infection and hematologic malignancy: A meta-analysis. Hepatology 2017;66:379–88.
[12] Pei SN, Ma MC, Wang MC, Kuo CY, Rau KM, Su CY, et al. Analysis of hepatitis B surface antibody titers in B cell lymphoma patients after rituximab therapy. Ann Hematol 2012;91:1007–12.

Masayo Yamamoto
Katsuya Ikuta
Koji Sawada
Motohiro Shindo
Yoshihiro Torimoto
Toshikatsu Okumura*
Division of Gastroenterology and Hematology/Oncology, Department of Medicine, Asahikawa Medical University, Asahikawa, Japan

* Corresponding author.
E-mail address: okumurat@asahikawa-med.ac.jp (T. Okumura)

8 November 2018

https://doi.org/10.1016/j.dld.2019.07.003
1590-8658/
© 2019 Editrice Gastroenterologica Italiana S.r.l. Published by Elsevier Ltd. All rights reserved.

Complete response of early stage hepatocellular carcinoma in a patient treated with combination therapy of camrelizumab (SHR-1210) and apatinib

Dear Editor,

Hepatocellular carcinoma (HCC) is one of the most common tumors with limited treatments and poor prognosis. Along with the discovery and researches of programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) and associated antibodies, the effectiveness of PD-1/PD-L1 inhibitor on the treatment of HCC is still controversial and remains as a research focus. Here we report a case of early-stage HCC with multiple times of recurrence and a poor response to sorafenib, having a complete response to the combination of camrelizumab (SHR-1210) and apatinib.

A 52-year-old male, having suffered from hepatitis B virus (HBV) infection and associated liver cirrhosis for 30 years, presented for the fifth time with continuously elevated alpha-fetoprotein (AFP) and recurrent tumors. Two years ago, the patient was initially admitted with continuously elevated AFP for 8 months. The imaging examination showed single tumor in S4b with diameter of 1.7 cm and then the patient was diagnosed with HCC, Barcelona Clinic Liver Cancer (BCLC) stage 0. Entecavir therapy for HBV infection had been administrated for 6 months before the admission. A curative liver resection was immediately performed and the patient was well recovered. After that, he received another curative liver resection during the second admission and a curative radiofrequency ablation (RFA) during the third admission respectively, due to tumor recurrence. In the fourth admission, the patient was diagnosed with recurrent HCC (BCLC stage B) and a drug-eluting beads transcatheter arterial chemoembolization (DEB-TACE) was performed. Besides, he took sorafenib 200 mg twice daily as an adjuvant therapy for 10 months until the fifth admission, which

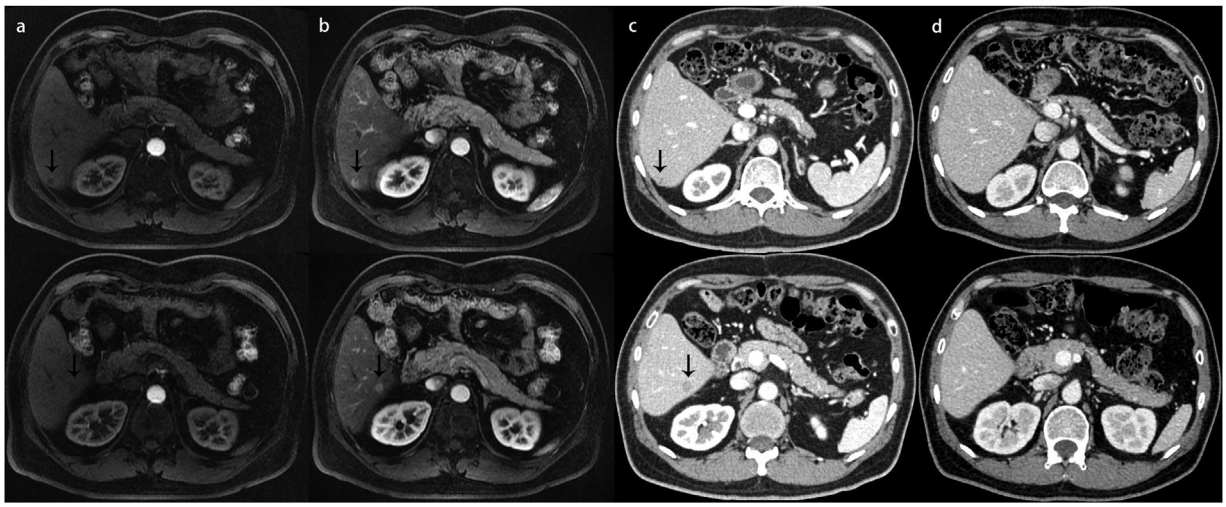

Fig. 1. a. Two tumors (black arrow) shown in arterial phase of MRI T1 sequence; b. two tumors (black arrow) shown in venous phase of MRI T1 sequence; c. contrast enhanced CT showed two tumors (black arrow) in the S6 of liver before the combination therapy; d. contrast enhanced CT showed tumor disappearance after 6 cycles of combination therapy. MRI, magnetic resonance imaging; CT, computerized tomography.

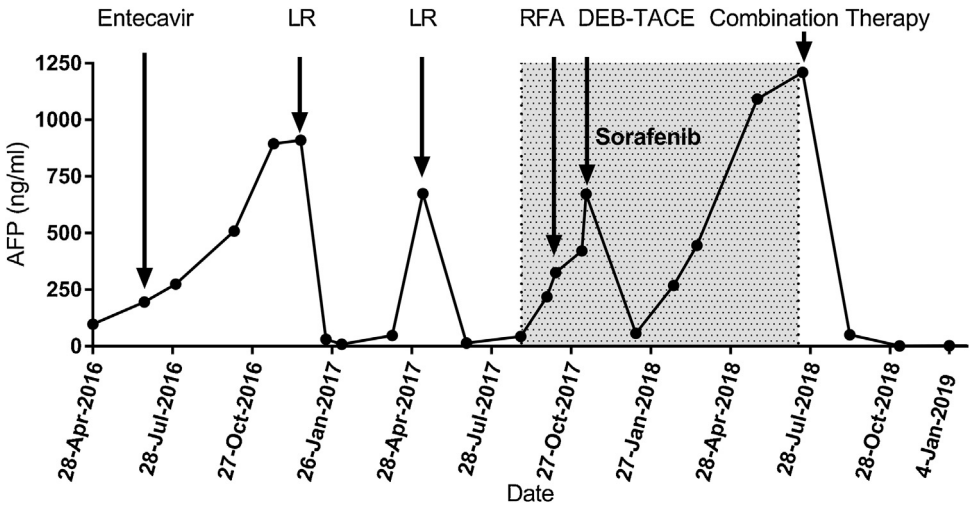

Fig. 2. The AFP level during the course of HCC. The AFP level had dramatically declined to the normal range and remained for almost 2 months after 6 cycles of combination therapy. The sequence of treatment is: Entecavir, LR, LR, Sorafenib, RFA, DEB-TACE, combination therapy. AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; LR, liver resection; RFA, radiofrequency ablation; DEB-TACE, drug-eluting beads transcatheter arterial chemoembolization.

was unfortunately proven to be invalid as the tumor continued to progress. His liver function remained normal after all these treatments.

The laboratory data revealed albumin = 48.9 g/L, total bilirubin = 8.4 umol/L, direct bilirubin = 3.2 umol/L, Alanine aminotransferase/Aspartate aminotransferase = 21.9/28.7 U/L, negative HBV DNA, prothrombin time (PT) = 13.6 s, international normalized ratio (INR) = 1.07, AFP level = 1210.0 ng/ml and Child–Pugh score = A5. Magnetic resonance imaging (MRI) and abdominal computerized tomography (CT) showed two tumor nodules in S6 with typical enhancement and largest diameter of 1.3 cm (Fig. 1). No metastasis was found in contrast enhanced CT scan of chest and brain. The patient was subsequently diagnosed with recurrent HCC (BCLC stage A4).

According to National Comprehensive Cancer Network guidelines of Hepatobiliary Cancers (Version 1. 2018 – February 14, 2018), another liver resection could be performed in this situation. However, the patient and his family strongly disapproved of any invasive treatment including surgery. With thorough evaluation and the patient's informed consent, a combination therapy containing camrelizumab and apatinib was administered in July 2018. Camrelizumab was given 200 mg fortnightly and apatinib 250 mg once daily for every 4 weeks as a cycle. After 6 cycles of treatment, a follow-up CT scan revealed a complete response (modified RECIST criteria) without any tumor activity (Fig. 1). Meanwhile, the level of AFP significantly decreased from 1210.0 ng/ml to normal (Fig. 2) and liver function remained normal (Child–Pugh score A5).

In terms of the adverse events, according to National Cancer Institute Common Terminology Criteria Adverse Events version 4.03 (NCI-CTCAE v4.03), the patient suffered from AE stage 2 hypothyroidism caused by camrelizumab, AE stage 2 hand-foot syndrome, hypertension, albuminuria, headache, gingival bleeding and AE stage 1 hematuria caused by apatinib, as well as AE stage 1 hypoleucocytosis as a result of both drugs. Overall, the side effects were tolerable.

In recent years, various immune checkpoint inhibitors have been extensively studied in various types of tumor [1]. In the phase I/II HCC nivolumab trial [2,3], the results were encouraging as objective response rate (ORR) of 20% with manageable safety profile in advanced HCC. In the open-label phase 2 pembrolizumab trial [4], 18 of 104 (17%) patients who had previously been treated with sorafenib experienced objective response with tolerable adverse effects. These trials showed significant potentiality of PD-1/PD-L1 inhibitor in treating HCC.

Furthermore, the combination of sorafenib and PD-1 blockade may provide synergic effects through relieving cell-intrinsic and cell-extrinsic inhibitions of effector T cells or the affection of vascular endothelial growth factor (VEGF), [5,6] indicating the combination therapy might become a prospective trend of immunotherapy. The recent phase I open-label study of SHR-1210 and apatinib combination therapy, starting from 2016, showed promising efficacy (ORR: 50%) in 16 patients with advanced HCC [7], which inspired us to administrate this particular treatment plan.

With the experience of the first case of successful combination therapy in early stage HCC, we have reasons to expect more patients with early-stage HCC could benefit from this combination therapy, which brings the question of whether we should expand the indication for immunotherapy. Future studies should be performed to answer this question.

Conflict of interest

None declared.

Guarantor of the article

The corresponding author is accessing to the data and have control of the decision to publish and accepting full responsibility for the conduct of the study.

References

[1] Heymach J, Krilov L, Alberg A, et al. Clinical cancer advances 2018: annual report on progress against cancer from the American Society of Clinical Oncology. J Clin Oncol 2018;36(10):1020–44.
[2] El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab 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):2492–502.
[3] El-Khoueiry AB, Melero I, Crocenzi TS, et al. Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): CA209-040. J Clin Oncol 2015;33(18_Suppl):A101.
[4] Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol 2018;19(7):940–52.
[5] Hato T, Zhu AX, Duda DG. Rationally combining anti-VEGF therapy with checkpoint inhibitors in hepatocellular carcinoma. Immunotherapy-UK 2016;8(3):299–313.
[6] Chen ML, Yan BS, Lu WC, et al. Sorafenib relieves cell-intrinsic and cell-extrinsic inhibitions of effector T cells in tumor microenvironment to augment antitumor immunity. Int J Cancer 2014;134(2):319–31.
[7] Xu J, Zhang Y, Jia R, et al. Anti-PD-1 antibody SHR-1210 combined with apatinib for advanced hepatocellular carcinoma, gastric, or esophagogastric junction cancer: an open-label, dose escalation and expansion study. Clin Cancer Res 2019;25(2):515–23.

Zeyu Zhang
Yufan Zhou
Kuan Hu
Zhecheng Li
Zhiming Wang
Yun Huang*
Department of Hepatobiliary Surgery, Xiangya Hospital, Central South University, Changsha, Hunan, China

* Corresponding author.
E-mail address: huangyun-1002@163.com (Y. Huang)

9 May 2019
https://doi.org/10.1016/j.dld.2019.07.005
1590-8658/
© 2019 Editrice Gastroenterologica Italiana S.r.l. Published by Elsevier Ltd. All rights reserved.

Sodium load and intravenous antimicrobials in patients with cirrhosis

Strong evidence indicates that reduction of salt intake lowers blood pressure and reduces the risk of cardiovascular disease and all-cause mortality [1]. This issue has also been deeply investigated in patients with decompensated cirrhosis. In fact, the guidelines of the European Association for the Study of the Liver (EASL) recommend a salt intake of 4.6-6.9 g/daily, corresponding to 1.84-2.76 g of sodium/daily, for patients with cirrhosis and ascites.[2] In the advanced stage of cirrhosis, splanchnic vasodilation causes a marked arterial underfilling that induces the maximum activation of the renin-angiotensin-aldosterone system, the sympathetic nervous system, and the arginine vasopressin release. All these activated systems would entail a reduced renal perfusion with consequent further retention of sodium and water, ultimately leading to the onset of hypervolemic hyponatremia and refractory ascites. The degree of activation of these neurohumoral mechanisms and renal impairment directly correlate with the degree of portal hypertension.[3] Consequently, hyponatremia represents a parameter indirectly reflecting the severity of portal hypertension, and it is strongly associated with an increased risk of liver-related mortality.[4] Furthermore, it has to be noted that any sodium intake (i.e., with food, or administered with fluid therapy such as balanced crystalloids, normal saline, colloids) in patients with cirrhosis may negatively affect the sodium retention being responsible for hyponatremia and worsening of ascites.[1]

Advanced stages of chronic liver disease favor the development of sepsis due to hepatic dysfunction, presence of porto-systemic shunts, intestinal dysbiosis, increased bacterial translocation, and immune dysfunction.[5] Therefore, the strategy to deal with the sepsis by extensive use of antibiotics treatment is mandatory in cirrhotic patients.[6] However, sodium is included in the preparation of the injectable antibiotics to stabilize the pH of the solutions, in varying amount according to the different classes of antibiotics.

Since sodium is the solute contained in the greatest quantity in the extracellular space, only 25-30% of the infused sodium remains in the intravascular space for 1-2 hours, whereas 70-75% very quickly flows into the interstitial space, contributing to maintenance of ascites and of peripheral edematous status.

Only a few, non-recent studies have taken into consideration the amount of sodium contained in the antibiotic solutions infused in patients with microbial infections and heart disease, and the possible impact of such unintentional administration of sodium on the heart failure.[7,8] This aspect has never been considered in the subset of patients with cirrhosis. In this regard, analyzing the amount of sodium contained in the antibacterial and antifungal treatments commonly recommended in patients with liver cirrhosis and microbial infections [5,9], a sodium concentration ranging from 12.05 mg to 7,680 mg was identified (Table 1).