



Editorial

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Is multidisciplinary treatment effective for hepatocellular carcinoma with portal vein tumor thrombus?

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Hepatocellular carcinoma (HCC) has aggressive biological characteristics and can invade the portal vein. The prognosis of patients with HCC with portal vein invasion is poor; if untreated, the median overall survival is only 2.7-4 months.¹

According to subgroup analyses of the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trials, when treated with sorafenib—the first-line therapy in patients with HCC with portal vein tumor thrombus (PVTT)—the median overall survival has been shown to be approximately 8 months.^{2,3} Treatment with regorafenib as second-line treatment has been demonstrated to extend survival by approximately 3 months.⁴ However, even with the same BCLC C stage, the extent of the PVTT may also affect the patient prognosis.⁵

Recently, HCC treatment approaches, such as hepatic resection, transarterial chemoembolization, radiation therapy, transarterial radioembolization (TARE) with yttrium-90, hepatic arterial infusion chemotherapy (HAIC), molecular targeted therapy, and immune therapy, have greatly advanced. Based on various retrospective clinical studies, it has been demonstrated that combination treatment or multidisciplinary management using the aforementioned treatments can improve the survival of patients with advanced HCC.⁶ However, there is no consensus or standard treatment strate-

gy for the multidisciplinary management of these patients.

The current issue of *Journal of Liver Cancer* reports several interesting cases which demonstrate that multidisciplinary treatments have improved the survival of patients with HCC with PVTT.

Cho et al.⁷ reported a case of a patient with advanced HCC with PVTT extending to the inferior vena cava (IVC) who was treated with intensity-modulated radiation therapy 1 year after sorafenib treatment. Since then, this patient has shown a complete response according to the modified Response Evaluation Criteria in Solid Tumors criteria following 27 months of sorafenib therapy. The rationale for combining sorafenib and radiotherapy is the known improvement of radiotherapy efficiency by blocking the Raf/MEK/ERK and VEGF recovery pathways using sorafenib. In addition, radiation followed by sorafenib therapy has been shown to be effective in delaying tumor growth.⁸ In this case, the tumor was an infiltrative HCC, and the tumor thrombus had invaded up to the IVC. Such patients are presumed to have a poor prognosis, regardless of the treatment they receive. After controlling the main tumor and the macrovascular invasion using sorafenib and radiotherapy, this case demonstrated a complete response after an additional 2 years of sorafenib therapy targeting latent microscopic disease.

Park and Yu⁹ reported a patient with infiltrative HCC with PVTT who received a combination of atezolizumab/bevacizumab dual therapy and TARE treatment. There was a mixed tumor response; the main mass decreased in size while lymph node metastases around the common hepatic artery showed progression. In theory, dual therapy with atezoli-

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zumab and bevacizumab combined with TARE, is more effective than sorafenib monotherapy. The reason for this is that the combination of TARE and immune checkpoint inhibitors may enhance local and systemic immune-mediated effects, and also trigger an abscopal phenomenon.¹⁰ Therefore, it is expected that treatment resistance could be better overcome than when providing treatment with TARE and immune checkpoint inhibitors individually. A phase II study of atezolizumab and bevacizumab in combination with TARE is currently underway (clinical trial information: NCT04541173).

Lee et al.¹¹ provided another report of a patient with HCC with PVTT who underwent combination treatment with atezolizumab/bevacizumab and HAIC. During treatment, the primary HCC decreased in size, but the PVTT increased in extent, and radiotherapy was provided. This report demonstrates a partial response to multidisciplinary treatment. The rationale behind the treatment in this case is similar to that of Park and Yu⁹—radiotherapy has been demonstrated to mediate localized tumor killing and to potentiate the tumor microenvironment modification provided by immune checkpoint inhibitors.

In the report by Kim et al.,¹² concurrent chemo-radiotherapy (CCRT) and HAIC was applied to a patient with HCC with PVTT. Subsequently, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) was performed. This was a two-stage surgical treatment after downstaging of advanced HCC with PVTT following CCRT and HAIC, and the patient experienced complete remission following multidisciplinary treatment. Although not applicable to all patients, this treatment can be recommended for patients with good liver function and sufficient nontumor liver volume.^{13,14}

These four case reports demonstrate relatively good outcomes of multidisciplinary treatment for patients with HCC and PVTT. However, because of the heterogeneity of the patient group, it is difficult to accurately compare and evaluate the efficacy of multidisciplinary management.¹⁵ In addition, despite the positive outcomes of these cases, the following limitations apply to most patients with HCC with PVTT who may benefit from multidisciplinary treatment. First, biomarkers that can predict which patient groups will benefit

from multidisciplinary treatment have not yet been established. Second, when applying combination treatment, it is unclear whether sequential or concomitant treatment is more effective. Third, although multidisciplinary treatment can lead to a complete response, it is uncertain when to stop using expensive immune checkpoint inhibitors or molecularly targeted therapies. Therefore, to demonstrate this, well-designed prospective or retrospective studies are needed to provide high-level evidence of the safety and efficacy of multidisciplinary treatment for HCC with PVTT.

Conflicts of Interest

Won Hyeok Choe has served on the Editorial Board of *J Liver Cancer* since July 2020. He was not involved in the review process of this article. Otherwise, the author has no conflicts of interest to disclose.

Ethics Statement

This editorial is fully based on the articles which was already published and did not involve additional patient participants. Therefore, IRB approval is not necessary.

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Data Availability

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Author Contribution

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References

1. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018;391:1301-1314.
2. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J*

- Hepatol 2018;69:182-236.
3. Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepatol* 2012;57:821-829.
 4. Altayar O, Shah R, Chang CY, Falck-Ytter Y, Muir AJ. AGA technical review on systemic therapies for hepatocellular carcinoma. *Gastroenterology* 2022;162:937-951.
 5. Mähringer-Kunz A, Steinle V, Düber C, Weinmann A, Koch S, Schmidtman I, et al. Extent of portal vein tumour thrombosis in patients with hepatocellular carcinoma: the more, the worse? *Liver Int* 2019;39:324-331.
 6. Salgia R, Mendiratta V. The multidisciplinary management of hepatocellular carcinoma. *Clin Liver Dis (Hoboken)* 2021;17:405-408.
 7. Cho Y, Kim BH, Kim TH, Koh YH, Park JW. Sorafenib combined with radiation therapy for advanced hepatocellular carcinoma with portal and hepatic vein invasion extending to the inferior vena cava: a complete response case according to modified RECIST criteria. *J Liver Cancer* 2022;22:63-68.
 8. Chen SW, Lin LC, Kuo YC, Liang JA, Kuo CC, Chiou JF. Phase 2 study of combined sorafenib and radiation therapy in patients with advanced hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2014;88:1041-1047.
 9. Park MK, Yu SJ. Concurrent transarterial radioembolization and combination atezolizumab/bevacizumab treatment of infiltrative hepatocellular carcinoma with portal vein tumor thrombosis: a case report. *J Liver Cancer* 2022;22:69-74.
 10. Sangro B, Sarobe P, Hervás-Stubbs S, Melero I. Advances in immunotherapy for hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol* 2021;18:525-543.
 11. Lee A, Lee J, Yang H, Sung SY, Jeon CH, Kim SH, et al. Multidisciplinary treatment with immune checkpoint inhibitors for advanced stage hepatocellular carcinoma. *J Liver Cancer* 2022;22:75-83.
 12. Kim IJ, Yoo SH, Lee JI, Lee KS, Lee HW, Lim JH. Long-term survival after CCRT and HAIC followed by ALPPS for hepatocellular carcinoma with portal vein invasion: a case report. *J Liver Cancer* 2022;22:84-90.
 13. Schnitzbauer AA, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann Surg* 2012;255:405-414.
 14. Schlitt HJ, Hackl C, Lang SA. 'In-situ split' liver resection/ALPPS - historical development and current practice. *Visc Med* 2017;33:408-412.
 15. Torimura T, Iwamoto H. Optimizing the management of intermediate-stage hepatocellular carcinoma: current trends and prospects. *Clin Mol Hepatol* 2021;27:236-245.