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

Won Hyeok Choe

Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Korea

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 chemembolization, 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 strategy 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 atezol-
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. 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. provided another report of a patient with HCC and 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 Yu - 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., 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 down-staging 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.

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. 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
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ORCID
Won Hyeok Choe https://orcid.org/0000-0002-8019-5412

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References
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