The Korean Journal of Hepatology 2010;16:353-354
DOI: 10.3350/kjhep.2010.16.4.353

Editorial

Which treatment modality should we choose for advanced hepatocellular carcinoma?

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The definition of 'advanced' hepatocellular carcinoma (HCC) has been vague and included various stages. This term has sometimes meant 'multinodular/unresectable HCC', 'HCC with vascular invasion', or 'HCC with extra-hepatic spread'. Since the introduction of the Barcelona Clinic Liver Cancer (BCLC) stage in 1999, the term 'advanced HCC' has been defined as a symptomatic tumor and/or invasive tumoral pattern (vascular invasion/extrahepatic spread).[1] Based on data suggesting limited efficacy of cytotoxic systemic chemotherapy and results from the SHARP trial,[2,3] sorafenib, a multi-kinase inhibitor, is now the only drug which has been shown to prolong the survival of patients with HCC with vascular invasion or metastasis.

Transarterial chemoembolization (TACE) is the standard of care for patients with multinodular HCC.[4] Although there is not a standardized procedure with different embolic or chemotherapeutic agents, different arterial selectivity before embolization, or different schedules and indications for repeated sessions,[5] TACE has been shown to be effective in prolonging survival compared to supportive care in randomized controlled trials and meta-analyses.[5,6] However, the outcomes of TACE depend upon patient selection. In a randomized trial which recruited HCC patients with compensatory cirrhosis, good performance status, and large or multinodular HCC with neither portal vein invasion nor distant metastasis, the 2-year survival rate was 63% compared to 27% for the untreated control group (P=0.009).[7] In another randomized trial, inclusion of patients with symptoms or limited portal vein invasion resulted in a 2-year survival rate of 31%.[6] In a subgroup analysis, TACE offered no survival benefit in patients with portal vein invasion. In addition to high rates of tumor recurrence or progression after the procedure, TACE promotes vascular endothelial growth factor (VEGF) production and subsequent angiogenesis. Therefore, apart from adverse events, the suboptimal anti-cancer effects of TACE observed when treating HCC with portal vein invasion may increase the chance of intra- or extra-hepatic spread of HCC.

Hepatic arterial infusional chemotherapy (HAIC) using low- or high-dose 5-FU and cisplatin for unresectable HCC has been established as a treatment option in Japan and several centers in South Korea. Despite several problems associated with HAIC such as subcutaneous port implantation and catheter placement, infection, and hepatic arterial occlusion with repeated therapies, promising HAIC anti-tumor effects without significant systemic adverse events have been reported in locally advanced HCC.[8,9] In a Japanese study, low doses of 5-FU (170 mg/m^2 on day 1-5) and low doses of cisplatin (7 mg/m^2 on day 1-5) were infused through a subcutaneously-implanted port in HCC patients with portal vein thrombosis.[8] After four courses of monthly HAIC, 4 (8.3%) and 19 (39.6%) out of 48 patients achieved complete response and partial response, respectively. In a Korean study in which high dose of 5-FU (500 mg/m^2 on day 1-3) and cisplatin (60 mg/m^2 on day) were administered, 9 (22.0%) and 14 (34.1%) patients exhibited a partial response and stable disease, respectively, without significant adverse events. The overall survival time was significantly longer in the disease-controlled group than in the disease-progression group (median of 14 versus 6 months, P <0.001).[10] There seems to be no difference in

Keywords: Hepatocellular carcinoma; Transarterial chemoembolization; Hepatic arterial infusion chemotherapy

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terms of efficacy between high- and low-dose regimens. A recent South Korean multicenter, randomized study showed that there was no significant difference in overall survival time (median of 193 versus 153 days, *P*=0.108), although the objective response rate was improved in the high-dose group compared to the low-dose group (16.7% versus 0%, *P*=0.024).[11] The presence of portal vein invasion without extra-hepatic spread is a clinical condition shared by repeated HAIC and systemic therapy using sorafenib. However, at present HAIC may not be generally recommended for treating advanced HCC because there has no randomized controlled study which shows a survival benefit of HAIC compared to sorafenib. Which transarterial therapy, then, is better for treating advanced HCC? A recent paper published by Kim et al. in *The Korean Journal of Hepatology* compared the treatment outcomes between high-dose HAIC and TACE in cases of advanced HCC.[12] Thirty-six patients in HAIC group had been recruited for another multi-center, prospective trial and 31 patients in TACE group were retrospectively selected from database of one institute. In this study, the objective responses (complete and partial responses) were significantly better in the group that underwent high-dose HAIC than in patients who received TACE (16.7% versus 0%, *P*=0.046). Overall survival was also better in the HAIC group compared to the TACE group (median survival times, 193 versus 87 days, *P*=0.028). The authors conclude that high-dose HAIC resulted in a better tumor response and survival outcome compared to conventional TACE using doxorubicin.

Strictly speaking, TACE and HAIC have different implications. Only selected cases of HCC with portal vein invasion are amenable to TACE. On the contrary, HAIC had been developed for treating more advanced HCCs, such as cases with diffuse involvement of both lobes or main portal vein invasion, which cannot be treated with TACE. Despite retrospective matching of tumor characteristics, it is unclear how many patients had infiltrative HCC, bilobar involvement, and main portal vein invasion in each group. Furthermore, since it appeared that gelfoam embolization had not been performed universally in the TACE group, actual comparison of HAIC and TACE in treating advanced HCC under the same tumor conditions might not have been done.

An important point of this study is that the effect of TACE monotherapy is a sub-optimal therapy for HCC with a substantial tumor burden, and so TACE is not beneficial in extensive (or diffusely involved) cases of HCC with or without portal vein invasion. For therapies for advanced HCC, we are armed with more treatment modalities than before. Besides HAIC, the efficacy of multimodal approaches with external beam radiation therapy, internal radiation with Yttrium-90, and combination therapies using sorafenib and other treatments for advanced HCC need to be validated by well-designed studies.[13,14]

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