Adding Sorafenib-eluting Microspheres to TACE: The Next Step in Hepatocellular Carcinoma Treatment

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Transarterial chemoembolization (TACE) is widely used to treat patients with inoperable hepatocellular carcinoma (HCC) and is also used as a “bridge” to liver transplantation to prevent excessive tumor growth while the patient is on the waiting list (1). The widespread use of this treatment option is supported by robust evidence that demonstrated increased overall survival with TACE compared with conservative management (2,3). Traditionally, this technique involves selective catheterization of the hepatic artery and infusion of a combination of chemotherapeutic drugs and embolic agents, with or without ethiodized oil. Frequent chemotherapeutic agents used are mitomycin and doxorubicin as a single agent or in combination. Common embolic agents used are absorbable gelatin sponge particles, polyvinyl alcohol, and microspheres.

More recently, TACE with drug-eluting beads (DEB-TACE) has been wildly adopted in many practices and involves the infusion of embolic microspheres loaded with doxorubicin. This allows more sustained local drug release in HCC because this is a notorious hypervascular tumor. Doxorubicin, the agent used in DEB-TACE, is approved for metastatic gastric cancer among other ones, including breast. It was only in 2008 that sorafenib was approved for systemic treatment of unresectable HCC based on a randomized controlled trial that demonstrated median overall survival of 10.7 months in patients who received sorafenib versus 7.9 months in the placebo group (5).

Sorafenib is an oral multikinase inhibitor that induces apoptosis and prevents cell proliferation and angiogenesis. This antiangiogenic effect is particularly important in HCC because this is a notorious hypervascular tumor. In addition, it is believed that residual and/or recurrent tumor after TACE is caused, among other factors, by the increased tumor neoangiogenesis triggered by the hypoxic environment created by embolization.

To overcome this, clinical studies have investigated the potential synergistic effect of TACE combined with systemic administration of sorafenib. In 2016, the SPACE trial randomly assigned 307 patients to receive DEB-TACE plus oral sorafenib or DEB-TACE alone (6). The primary endpoint of progression-free survival was not met, and neither was time to unTACEeasable progression (TTUP), a novel endpoint (95 vs 224 days; hazard ratio, 1.586; 95% CI: 1.200, 2.096; \(P = .999\)). However, a recent randomized controlled trial (TACTICS) with similar design of the SPACE trial demonstrated a statistically significant increase in TTUP in the group that received TACE plus oral sorafenib compared with the group that received only TACE (25.2 vs 13.5 months; hazard ratio, 0.59; 95% CI: 0.41, 0.87; \(P = .006\)) (7). The authors believe the difference in the results can be attributed to the longer period of sorafenib administration (38 weeks vs 21 weeks) and longer exposure to sorafenib before TACE (4 weeks vs 3–7 days) in the TACTICS trial compared with the SPACE trial.

Although TTUP is not a classic endpoint used to evaluate treatment efficacy, the TACTICS trial indicates clinical benefit of this synergistic approach. Therefore, given the robust evidence supporting TACE in the treatment of HCC as mentioned before, the next logical step would be the intra-arterial administration of sorafenib, a chemotherapeutic agent with specific Food and Drug Administration approval for HCC. In that regard, the authors of a preclinical in vivo
study looking at the infusion of sorafenib-eluting microspheres (SOR-EMs) in rats with HCC made a tremendous contribution to the advancement of HCC treatment (8).

The study compared groups of rats with HCC treated with different combinations of intra-arterial infusions: doxorubicin-lipiodol emulsion (DLE); DLE plus embolic microspheres; DLE plus SOR-EM; and saline infusion only. The statistically significant increase in apoptosis rate and decrease in vessel density seen in tumors of rats treated with DLE plus SOR-EM is very reassuring of the utility of this new approach. In addition, the significant reduction in tumor size seen in those rats confirms the efficacy of this technique. This is critical for the potential clinical application of this approach because tumor response assessed by cross-section imaging is a prognostic factor in patients with HCC, with patients achieving complete response having a favorable prognosis.

Despite the results, it is worthy of commenting on the technique applied. Although the study was designed to analyze the synergistic effect of conventional TACE and local infusion of sorafenib, the initial infusion of DLE prior to SOR-EM could have prevented the full local delivery of sorafenib. It is well known that the ethiodized oil used to create the DLE has an embolic effect, and the tumor vasculature could have already been saturated before the infusion of SOR-EM. This can lead to future studies looking into the efficacy of the infusion of only sorafenib-eluting beads to allow full delivery of this Food and Drug Administration-approved agent to the tumor. Furthermore, this could be done with permanent embolic microspheres and not biodegradable microspheres as utilized in this study. In that way, the permanent embolic agent would promote tumor necrosis by ischemia, while sorafenib would prevent neangiogenesis triggered by the hypoxemic environment.

Finally, the landscape of systemic treatment for HCC is rapidly changing with new classes of agents becoming clinically available in the last few years. This opens the door for potential utilization of these drugs during intra-arterial treatment of HCC as the primary chemotherapeutic agent. In addition to sorafenib, other multikinase inhibitors, such as regorafenib and lenvatinib, have shown similar efficacy in terms of overall survival. Moreover, immune checkpoint inhibitors, including nivolumab and pembrolizumab, is another class of drugs recently added to the armamentarium against HCC (9).

As mentioned before, this current study adds essential information for the future direction of the treatment of HCC, which is still a leading cause of cancer-related deaths worldwide, with a majority of patients being diagnosed at an advanced stage when treatment options are limited.

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