RE: Roles Played by Chemolipiodolization and Embolization in Chemoembolization for Hepatocellular Carcinoma: Single-Blind, Randomized Trial

We read with great interest the paper published by Shi et al. comparing three different regimens of transarterial therapy for unresectable hepatocellular carcinoma (HCC) (1). It is encouraging to notice that aggressive triple-agent chemolipiodization, with or without embolization, is associated with an improvement in overall survival (OS), compared with single-agent transarterial chemoembolization (TACE). We would like to highlight three areas for further discussion.

In the Shi et al. study, the population was made up of heterogeneous populations, consisting of those with Barcelona-clinic liver cancer (BCLC) stage B (65.5%) and C (34.5%) disease. It is noteworthy that the median OS of patients with BCLC stage C disease is only 5.4 months, which is no better, but in fact worse, than the OS of patients in Asian phase III clinical trials on sorafenib (6.1 months) (5) or systemic doxorubicin (6.8 months) (6). Although cross-trial comparison is not always feasible, the latter two trials were primarily designed for patients with more advanced disease. For example, more than 30% of patients had extrahepatic metastases in the sorafenib trial (5), and more than 10% of patients had Child's B cirrhosis in the clinical trial on systemic chemotherapy (6), compared with none in the Shi et al. study. Considering this factor, the OS of patients with BCLC stage C disease observed in the Shi et al. study is considerably lower than expected, and this may have confounded the comparison to the triple-agent transarterial regimen.

In addition, the survival benefits of TACE have only been demonstrated in highly selected populations in previous phase III clinical trials (2,3), and determining who are the optimal candidates for unresectable HCC for TACE remains controversial. Some clinicians emphasize the lack of choices of systemic agents and prefer to administer TACE whenever technically feasible, whereas others opt to recommend systemic agents to a subgroup of patients with high tumor burden or portal vein thrombosis because of a historic poor response to TACE in these patients (4). The suboptimal survival of patients with BCLC stage C disease or with portal vein thrombosis, as demonstrated by the Shi et al. study, should have challenged whether transarterial therapy remains the answer for these groups of patients.

Finally, the article did not mention the time schedule and criteria for retreatment with study transarterial procedures. It is noted that most study participants in the Shi et al. study received less than two cycles of study TACE sessions (mean = 1.61). However, patients in the triple-agent transarterial regimen arms received more second-line treatments, including surgery, routine TACE, and radiofrequency ablation, than those in the single-agent TACE arm. It is possible that the better OS observed in the triple-agent transarterial therapy arm is a result of more intensive second-line treatment rather than a result of the study's transarterial therapies. In fact, the virtually identical and relatively short time-to-progression (3.1–3.6 months) observed across the three arms make this postulation more plausible.

In summary, we concur with Shi et al. that embolization probably plays a less important role when the transarterial regimen consisting of three-agent chemotherapy is used. Whether triple-agent transarterial therapies should be administered to all patients with unresectable HCC remains to be evaluated.

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DOI: 10.1093/jnci/djt047

Advance Access publication March 15, 2013

Response

We appreciate the thoughtful comments of Dr Chan et al. with respect to our recent publication.

Chan et al. noticed that the survival of patients in our study was lower than that in previous two trials (1,2). However, we think that our results were not comparable with those two. First, it is well known that intrahepatic tumor size is one of the most important prognostic factors for survival in hepatocellular carcinoma (HCC) patients (3,4). Our study was primarily designed for patients with huge intrahepatic tumors (median tumor size = 10.9 cm; range = 7–22 cm), whereas those two trials were not. And in Cheng et al.'s study (2), only patients