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TACE with or without systemic therapy?

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Transarterial chemoembolisation (TACE) delivers a chemotherapeutic agent (usually doxorubicin) into the feeding vessels of a hepatocellular carcinoma (HCC) and blocks the subsequent perfusion of these vessels by the injection of a plugging material. Two randomized controlled trials, conducted 10 years ago, reported a survival advantage for patients with a preserved liver function [1,2]. Subsequent meta-analysis confirmed that TACE increased the survival of patients with HCC [3,4]. TACE is a particularly attractive option for the management of patients with HCC because it is associated with few side effects and requires no more than a 24-h hospitalization. Until recently, TACE was a notoriously heterogeneous procedure with variable outcomes. The demonstration that the delivery of small beads loaded with doxorubicin was associated with fewer systemic side effects led to a standardization of the TACE procedure [5]. TACE is offered to patients in stage B of the Barcelona classification, which represents the largest fraction of patients seeking treatment. Therefore, improvements of TACE therapy are a matter of urgency.

TACE has two intrinsic limitations: it treats only the tumor tissue dependent on the embolized vessels and it elicits a reaction of growth factors. HCC sustains its growth by angiogenesis; specifically by promoting the formation of blood vessels from surrounding arteries. Although TACE embolizes the principal feeding arteries of the tumor, it leaves smaller vessels open, which explains why the procedure is palliative and not curative. Moreover, in cases of multifocal HCC with foci too small to be radiologically visible, TACE does not treat these additional lesions. In fact, it may even promote their growth [6]. Therefore, one improvement would be to prevent the recruitment of these secondary vessels. TACE induces a central anoxia with a peripheral hypoxia. This hypoxic stress provokes cells to release angiogenic growth factors. It is well documented that the circulating levels of VEGF increase after TACE [7,8]. Nowadays these limitations of TACE can be alleviated. Systemic antiangiogenic therapies have been developed, exemplified by sorafenib, which has been approved for the systemic treatment of HCC. Although attractive in theory, the combination of sorafenib with TACE could be associated with more side effects, such as abscesses. A phase I study tested the safety and feasibility of combining sorafenib with TACE, beginning the systemic treatment a week before the first TACE and without stopping the drug during the TACE sessions [9]. This study was not associated with major side effects opening the field to phase II studies.

In this issue of the *Journal*, Joong-Won Park and co-workers report the results of a single-center phase II, open-label, single-arm study combining sorafenib with TACE in 50 patients [10]. Ninety-four percent were Child–Pugh class A, 70% were treated with surgical or locoregional therapies before enrollment. Sixty percent received the concurrent treatment as planned for 24 weeks. The most common reasons for discontinuation of sorafenib was HCC progression (17 patients), and for only 1 patient, adverse event. The authors report an overall median time to progression of 7.3 months for the 41 patients BCLC stage B and of 5.0 months for the 9 patients in BCLC stage C. The 6-month progression-free survival rate was 52%. The authors conclude that the increased survival is an improvement when compared with historical control patients treated only with TACE. Given the heterogeneous characteristics of the patients included and of the historical control population, it remains impossible to infer that the combined treatment from this trial is more efficacious. Moreover, this trial was designed such that the systemic therapy with sorafenib was withheld for the TACE sessions and reintroduced on day 3 after the procedure or delayed further in case of major laboratory abnormalities. This prudent scheme was selected to avoid an augmentation of post-TACE complications with sorafenib. Nevertheless, it might have been deleterious because of tumor rebound after sorafenib interruption, as has been observed in animal models [11]. Moreover, the concentration of VEGF peaks on the day following TACE [7]. Therefore, in contrast to a continuous scheme, this scheme denies sorafenib at the time it is the most needed [12].

Additional studies have tested sorafenib in combination with TACE. Erhardt presented a trial with a similar, interrupted design, but enrolled 45 treatment naive patients and performed lipiodolization rather than embolization [13]. The overall survival was 20 months. Unfortunately, the lack of a control group limits the interpretation of the survival, which is not beyond the expected range for patients treated with TACE only. The clinical community awaits the results of the ECOG E1208 phase III trial, which has included a control group, to better appreciate the potential and limitations of interrupted combination (NCT01004978).

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Pawlik *et al.* recently published the findings of a study with 35 advanced HCC patients, most of them BCLC stage C, and continuous administration of sorafenib [14]. They report disease control in 95% of the patients using the Response Evaluation Criteria in Solid Tumor (RECIST). The lack of a control groups renders interpretation difficult. The large phase II SPACE trial randomized 307 patients for sorafenib or placebo. Sorafenib was given continuously and TACE was performed with drug-eluting beads. The hazard ration for time to progression was 0.797 and reached the predefined statistical level [15]. Nevertheless, the effect was modest, with a median time to progression of 169 days in the sorafenib group *vs.* 166 days in the placebo group.

Taken together, these trials confirm the phase I study showing that the combination of sorafenib with TACE is associated with manageable side effects. However, these results underline the necessity to collect good quality clinical data on the combination of systemic targeted therapy with TACE in order to design clinical trials optimizing enrollment criteria and end points to capture the magnitude of the effect. In particular, the transient perturbation of the laboratory results occurring after TACE should be carefully integrated. Finally, if sorafenib has the advantage of proven efficacy in monotherapy, trials are testing the combination of TACE with other antiangiogenic systemic therapies such as brivanib (NCT00908752) or everolimus (NCT01009801). In particular, everolimus lowers circulating VEGF levels, in contrast to sorafenib which increases them [16].

Conflict of interest

The author declare that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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