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TACE treatment in hepatocellular carcinoma: What should we do now?

To the Editor:

We read with much interest the comment by Forner *et al.* [1] on the recently published Cochrane review on Transcatheter Arterial (Chemo) Embolization (TACE/TAE) treatment in hepatocellular carcinoma by Oliveri *et al.* [2]. The debate on the effectiveness of TACE in patients with intermediate stage hepatocellular carcinoma (HCC) is still open, indeed. On the one hand, as summarized in the updated American Association for the Study of Liver Diseases (AASLD) guidelines, there is no doubt that the level of evidence on the efficacy of TACE in the treatment of intermediate stage HCC is strong (IA, according to the standard evaluation [3], with a consequently strong grade of recommendation [Grade A]). On the other hand, there is also no doubt that this strength lies basically on the results of two randomized prospective studies [4,5] that deeply condition the two meta-analyses published on the topic [6,7]. Nevertheless, TACE is also supported by the fact that it is used in the everyday clinical practice of every center involved in the management of HCC, a very low level (IV), but still important, evidence.

Dr. Forner correctly underlines that one of the papers quoted in Olivieri's meta-analysis, the Doffoel's randomized prospective trial of TACE *vs.* tamoxifen [8], presents many biases and includes patients that may have been "sub-optimally staged, selected and/or treated". In several French studies, indeed (see also the two Pelletier's articles [9,10]), the survival after TACE is so short that being affected by an intermediate stage HCC in France at the end of the last century would have suggested to move to other countries for treatment. Indeed, the reported 1-year survival (ranging from 25% to 50%) was not considered acceptable elsewhere and in past years those two studies heavily conditioned the clinical evaluation of TACE as a treatment for patients with multinodular HCC.

The Cochrane review in any case casts new doubts on the topic, doubts that induce to wonder what to do in patients with intermediate stage HCC, if one accepts the conclusions of the review. In our experience, based on the data (prospectively collected over 20 years) of the ITA.LI.CA database, patients with intermediate stage HCC treated by TACE present a median survival of 35 months (42 months in those treated in the last decade), with 1- and 5-year survivals of 80% and 18%, respectively. Having said this, it is worth noting that only a fraction of patients with an intermediate stage HCC were treated by TACE, while in the other cases, the treatment options vary from surgery or percutaneous treatments to best supportive care, depending on a number of factors not considered in the Barcelona Clinic Liver Cancer (BCLC) algorithm, such as age, co-morbidities, patient's decision, and local expertise, particularly, as far as the availability of highly experienced surgical teams is concerned. Interestingly enough, patients with intermediate stage HCC who can be treated more aggressively tend to survive longer than those treated by TACE (median survival of 52 months and 5-year survival over 30%). Our, still unpublished, data clearly demonstrate that TACE should not be abandoned, remaining the standard of care, in clinical practice, for most patients with intermediate stage HCC. However, the indication to TACE should not be automatic and, if the patients are considered eligible for more aggressive treatments, in a multidisciplinary approach also including percutaneous ablation and surgery, an even better survival can be obtained. Nowadays, there is indication for a combined/sequential tailored treatment, with a strategy that involves hepatologists, interventional radiologists, and surgeons. Likely, in the near future an adjuvant treatment with sorafenib or new anti-angiogenetic molecules will be part of this strategy.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Fabio Farinati*
Anna Giacomin
Veronica Vanin
Department of Surgical and Gastroenterological Sciences, Section of Gastroenterology, University of Padova, Padova, Italy
For the ITA.LI.CA (Italian Liver Cancer) group
*Corresponding author. *Tel.: +39 049 8211305; fax: +39 049 8212887*
E-mail address: fabio.farinati@unipd.it

Edoardo Giannini
Section of Gastroenterology, Department of Internal Medicine, University of Genova, Genova, Italy
For the ITA.LI.CA (Italian Liver Cancer) group

Franco Trevisani
Department of Clinical Medicine, Alma Mater Studiorum-University of Bologna, Bologna, Italy
For the ITA.LI.CA (Italian Liver Cancer) group

Sorafenib prolongs survival, but what happens to the symptoms?

To the Editor:

A recent review published in the *Journal of Hepatology* discusses the opportunities for chemotherapy in hepatocellular carcinoma (HCC) [1]. In this review, the authors conclude that "*Sorafenib is currently regarded as the standard of care in selected patients with advanced HCC based on two large randomised placebo controlled trials*" [2,3]. Furthermore, the introduction suggests its use as a palliative therapeutic. But what actually defines a palliative treatment? A decent definition of palliative chemotherapy is given by V.R. Archer in 1999: "*Palliative chemotherapy is defined as treatment in circumstances where the impact of intervention is insufficient to result in major survival advantage, but does affect improvement in terms of tumor-related symptoms, and where the palliation/toxicity trade-off from treatment clearly favors symptom relief*" [4].

Assuming sorafenib to be a palliative treatment, the data of the SHARP [2] and the Asian Pacific Trial (APT) [3] can be used to extrapolate the medians of asymptomatic and symptomatic time of survival. In both studies, the eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less (i.e. ranging from full active: 0, to capable of self-care but unable to work: 2) [5]. It thus seems fine to assume that the patients entered the study with a preserved quality of life. Furthermore, both studies give data for the cut-off, where an asymptomatic patient changes to a symptomatic one: the time to symptomatic progression (TTSP). Both studies defined symptomatic progression (SP) as death, a decline to an ECOG performance status score of 4 (i.e. completely disabled, confined to bed, and chair) [5] or an increase of 4 points in the Hepatobiliary Symptom Index (FISH-8) questionnaire [6]. Last but not least, both studies also report overall survival.

The SHARP trial reported a median overall survival (OS) of 10.9 months *vs.* 7.9 months for sorafenib *vs.* placebo respectively (p <0.001), and a median time to symptomatic progression of 4.1 months *vs.* 4.9 months (p = 0.77) [2]. The APT reported a median OS of 6.5 months *vs.* 4.2 months for sorafenib *vs.* placebo (p = 0.14), and a median TTSP of 3.5 months *vs.* 3.4 (p = 0.50) [3]. Assuming that patients were asymptomatic at the beginning of the study, the majority of patients remained asymptomatic until the median of TTSP was reached. Beyond this, the majority of patients was symptomatic and stayed so until the median of overall survival was reached (Fig. 1).

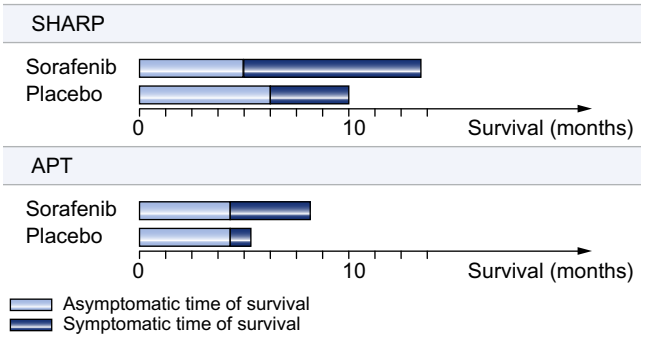

Fig. 1. The upper part shows the results of the SHARP-trial, the lower part shows the results of the APT. The bars are showing the median time from study entry to symptomatic progression (light blue) and, further on, to median overall survival (dark blue).

While sorafenib definitely marks a milestone in the treatment of non-resectable HCC, both trials only show a prolongation of survival with minimal to no impact on the time to symptomatic progression (in both trials, this outcome was non-significant). Even thought sorafenib may not reflect the characteristics of an ideal "palliative drug", a patient's wish for treatment in the setting of non-curable disease should never be underestimated. For example, in 104 women with breast cancer who already had three cycles of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) as adjuvant treatment, the patients were asked to rate the survival benefit that would justify 6 months of such a treatment. Surprisingly, 50% of all patients would participate in another 6 months of treatment for a small 1% gain in 5 year-survival [7].

Thus, the prescribing doctor and his or her patients should be aware that while sorafenib may prolong the median survival of 2–3 months [2,3], the symptoms associated with the disease or its treatment remain untouched. For patients in whom the main desire is for a treatment "to buy them some time", sorafenib remains a good option. However, the patient must then be aware of all the possible adverse events, the possible longer symptomatic course, and the substantial costs of the treatment involved (about 2400 EUR per month). In the end, treatment deferral also remains a valid choice and accepting the natural course of a disease may indeed be the best option for some