Combined strategies for hepatocellular carcinoma treatment: a new hope

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Hepatocellular carcinoma (HCC) is the most common tumor of the liver and the third cause of cancer death worldwide (1). Noteworthy, HCC incidence has increased in the last decades, and mortality rates are still rising among many population groups (2). Despite the efforts in order to detect the disease in its early stages, most tumors are only diagnosed after achieving significant dimensions or local/systemic complications. The Barcelona Clinic Liver Cancer Staging system (BCLC) is one of the most used classifications to stratify patients according to estimated survival, also suggesting the treatment options that should be conducted in each stage based on prior clinical evidences. The system proposes that liver tumors beyond the criteria for curative treatment should be graded as intermediate (B), advanced (C) and end stage (D) (3). Only patients with early stage HCC are candidates for curative treatments, whereas those with intermediate and advanced tumors should receive palliative treatments such as transarterial chemoembolization (TACE) and sorafenib, respectively (3,4).

There are many treatment options available for HCC but the best choices for intermediate and advanced tumors are sometimes a matter of controversies (5). Even patients in the same BCLC stage can be very dissimilar, because most of them have two diseases: liver cirrhosis and HCC. Hence, patients in the intermediate stage can present different degrees of liver impairment, and their tumors can vary in number, dimensions and radiological classifications, leading to multiple disease combinations.

The same differences can be observed in the advanced stage, making it difficult to compare the different outcomes in a single treatment choice. It has leading researchers to propose strategies that differ from those suggested by the current guidelines. For instance, patients in intermediate and advanced HCC stages have been submitted to curative treatments such as liver resection, sometimes achieving excellent results (6-9).

One can say that the good outcomes observed in studies on HCC patients who underwent surgical procedures are a consequence of the improvement in surgical techniques in the last years. Although this is a relevant point to be addressed, there is no doubt that the heterogeneity of these patients takes part of these results, allowing the authors to include only well selected patients in some clinical trials while different results are found when the selection is not so strict. The differences between patients in the same BCLC stage lead some authors to propose subclassifications for a better choice between the available treatments. Thus, patients with intermediate HCC should be included in one of four additional stages (B1-B4), and the same should be done for patients with advanced HCC (C1-C4) (10,11). These systems are an attempt to help clinicians in making difficult decisions regarding the treatment of patients not in the early stage.

The heterogeneity of patients and results of well-known clinical trials have shown a clear message: some patients can be submitted to more aggressive treatments than those proposed in the BCLC staging system, and taking these more aggressive treatments can lead to better results. However, taking these treatments can increase the risk of complications. Not all patients with intermediate and advanced HCC stages can undergo curative procedures

with an acceptable risk rate, making a careful selection of patients the first step in obtaining good results.

Nevertheless, if not too many patients in these stages can undergo a curative treatment, a substantial amount of them may be able to receive more treatment options than those proposed in the BCLC system, with acceptable risks and significant chances of achieving better survival rates.

Focusing on those better results, many authors have conducted clinical studies combining different treatment strategies. This has been done in patients with early stage HCC by sometimes adding strategies proposed for other stages, such as TACE or sorafenib (12-14). Similar approaches have been used for intermediate and advanced stages, in search for better chances of prolonged survival. The majority of the studies have looked into the most widely employed strategy for unresectable HCC, which is TACE and sorafenib combination.

Despite the amount of articles reporting good results using this combination, its efficacy is still debatable because the studies have included dissimilar patients who underwent different approaches. Four meta-analysis articles have shown that the combination is useful, but increases the incidence of adverse effects (15-18). While some studies included only Child-Pugh A patients with intermediate HCC and low levels of alpha-fetoprotein, others included a more heterogeneous sample, leading to more contrasting results. In addition, some studies had strict protocols in which TACE and sorafenib had to be prescribed together, while others had a more flexible approach in which they were performed subsequently (19-21).

Varghese and collaborators evaluated the benefits of combining TACE and sorafenib for patients with intermediate and advanced HCC stages. Most subjects had viral hepatitis, non-alcoholic steatohepatitis and cryptogenic cirrhosis, and few of them had alcoholic liver disease. Those with total bilirubin higher than 3 mg/dl or Child-Pugh C cirrhosis were excluded, and the maximum tumor size was 7 cm (22). These sample characteristics are the first reason to the successful outcomes obtained. Patients with alcoholic addiction tend to be malnourished and more prone to develop complications (23). Those with Child-Pugh C cirrhosis would be graded as end-stage HCC according to the BCLC system (3). Safety concerns would be expected if the authors had submitted patients with too large tumors to TACE (24). Even so, the study was not limited to Child-Pugh A patients with small tumors and included a real-life sample, establishing reasonable inclusion/exclusion criteria.

The second reason leading to the good results in the study of Varghese *et al*. was the study protocol. Instead of administrating both treatments at the same time, the authors introduced sorafenib 5 days after TACE, when tumor angiogenesis was expected. Moreover, the subjects have initially received a sorafenib half dose regimen (200 mg twice a day). Only patients showing good tolerance to the initial dosage were submitted to the 400 mg bid dose. In a prior trial in which the drug was initiated before TACE, the study had to be prematurely stopped because of safety concerns (21).

A third reason for the results obtained in the study were the endpoints assessed. The outcomes in the overall cumulative probability of survival were remarkable, but the authors also evaluated tumor response, which was measured through the Modified Response Evaluation Criteria In Solid Tumors (mRECIST) criteria. Some HCC characteristics are different from other solid tumors, such as the development of arterial contrast enhancement, an in-treatment goal that makes the mRECIST criteria more adequate to measure local response (25-26).

The message of Varghese *et al*. study is clear: if the patients are well selected, they can receive combined treatment modalities to achieve better outcomes. On the other hand, it is important to remember that some of the patients will face severe adverse effects, and they have to be prepared to it by being alert of the risks and the possible advantages. The second step is to establish an individualized approach, because when the boundaries proposed by the guidelines are crossed, risks may increase. The finding of the safest strategies for the best results require us to perform similar studies using the substaging of intermediate and advanced HCC, combining reasonable patient selection with personalized approaches.

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