Target Therapy for Hepatocellular Carcinoma: Is Sorafenib for Everybody?

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Hepatocellular carcinoma (HCC) is a relevant health problem, being the sixth most common cancer worldwide in terms of incidence with 626,200 new cases per year, accounting for 5.7% of all new cancer cases.[1] Due to the poor prognosis of the disease, the number of deaths per year is almost the same as new cases (598,000), making HCC the third most common cause of cancer-related death.[1]

Prognosis and feasibility of treatments for HCC patients largely depend not only on tumor characteristics, but also on the severity of the underlying chronic liver disease that affects the majority of cases.[2,3] Prognosis is relatively better for the subset of patients eligible for surgery (tumor resection or orthotopic liver transplantation) or for local ablation strategies with potentially curative aim (eg, percutaneous ethanol injection or radiofrequency ablation). Outcome is significantly worse for those patients who can be treated only with palliative locoregional treatments, such as transcatheter arterial chemoembolization (TACE), or who are affected by advanced disease. Unfortunately, curative strategies are currently limited to a minority of patients, those who present at diagnosis with small nodules, disease confined to the liver, good performance status, and well preserved liver function. The proportion of patients presenting with these characteristics is currently no more than about 30% to 40%.[4] In the experience of the Cancer of the Liver Italian Program group, in a series of 650 patients diagnosed in the years 1994 to 1999, 59% of patients at diagnosis were not treatable by surgery or percutaneous ablation.[5] However, the proportion of small, early tumors is expected to significantly increase in the next years, together with the diffusion of surveillance procedures of high-risk patients, allowing tumor diagnosis at an earlier stage.[4]

Although HCC can be considered a common cancer, evidence about best treatment options is currently based on a disappointingly limited number of randomized controlled trials, compared to many other solid tumors. This is especially true for systemic therapy, which has been associated with low response rates and no survival benefit, partly because HCC is a chemotherapy-resistant tumor[6]—due to the expression of the multidrug resistance gene MDR-1[6–8]—and partly due to the underlying liver cirrhosis in most patients, which prevents the administration of full dosage of many drugs. In addition, the majority of controlled clinical trials of systemic therapy in this patient population are flawed by inappropriate end points and controls, as well as by inadequate sample size.

Therefore, the results of the SHARP trial, a phase III prospective, randomized and placebo controlled trial of sorafenib in patients with advanced HCC were welcomed with enthusiasm, both for the quality of the study design and for its positive results.[9] In this trial, sorafenib improved survival and progression-free survival of patients with advanced HCC and Child A liver cirrhosis. On the basis of these results, both US and European Drug Regulatory Agencies, Food and Drug Administration (FDA) and European Medicines Agency (EMEA), authorized the marketing of sorafenib for the treatment of "unresectable hepatocellular carcinoma" (FDA) (*http://www.fda.gov/cder/foi/label/2007/021923s004s005s006s007lbl.pdf*) or just "hepatocellular carcinoma" (EMEA) *(http://www.emea.europa.eu/humandocs/Humans/EPAR/nexavar/nexavar.htm*).

Are these wide indications appropriate in the light of available data? Probably not. The broader EMEA indication allows prescription of sorafenib to all patients with HCC, irrespective of the stage of liver cirrhosis and cancer. However, there is no data whatsoever on the efficacy of sorafenib in patients with early HCC, both alone or in association with the commonly used locoregional treatments (ie, surgical resection, percutaneous ablation procedures, TACE). Indeed, at least 2 studies are exploring the role of sorafenib in less advanced settings, either in association with surgery or percutaneous ablation procedures (STORM trial: Sorafenib as Adjuvant Treatment in the Prevention Of Recurrence of Hepatocellular CarcinoMa) (*http://clinicaltrials.gov/ct2/show/NCT00692770?term = storm+*

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trial&rank = 1) or in association with TACE (*http://www.controlled-trials.com/ISRCTN24081794/*) and the results will be available not before several years. The FDA indication is somewhat more restrictive, in that it excludes from sorafenib treatment HCC patients that can be surgically resected or transplanted, although the same above considerations hold true for the association of sorafenib with percutaneous ablation procedures or TACE. Both the EMEA and the FDA indications do not limit the prescription of sorafenib to Child A patients, which represent most of the HCC patients in the SHARP trial (Only 20 Child-Pugh B patients out of a total of 601).[9]

In this issue of the Journal, Worns et al present data on the outcome of 34 patients with advanced HCC and different degrees of liver failure treated with sorafenib.[10] Although the study has some limitations—that is, the small number of patients and the lack of randomization—its results show that sorafenib is not tolerated as well in Child-Pugh B and C patients as in Child-Pugh A patients. First, diarrhea and some skin toxicities such as dry skin or rash/desquamation were more frequent in patients with Child-Pugh C liver cirrhosis. Second and more important, the 19 patients with more advanced liver cirrhosis (mainly Child-Pugh B) showed a higher incidence of grade 3 to 4 liver toxicity than Child-Pugh A patients and needed to discontinue treatment in a large percentage of cases (40% in Child-Pugh B and 50% in Child-Pugh C patients). This large incidence of liver toxicity may well depend on the progression of the liver disease, rather than on sorafenib toxicity, although caution has been suggested when administering sorafenib in patients with increased serum bilirubin[11] or with HCC and Child-Pugh B liver cirrhosis.[12] This question can be addressed only in a dedicated prospective trial,[13] which could also help select, within the heterogeneous class of Child-Pugh B patients with HCC, subgroups that may benefit more from sorafenib therapy. This trial, however, will be difficult to run as long as the drug regulatory Agencies allow the use of sorafenib in patients with HCC and any degree of liver failure. Meanwhile, waiting for more safety data, based on the natural history of patients with liver cirrhosis and on the very limited data of sorafenib in patients with more advanced liver disease,[9,10,12,14] we believe that, despite of the broad indications of both FDA and EMEA, sorafenib should not be used in patients with HCC and Child-Pugh C liver cirrhosis, while extreme caution is needed when using the drug in patients with HCC and Child-Pugh B liver cirrhosis.

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