

# HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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## Sorafenib in Combination With Transarterial Chemoembolization for the Treatment of Hepatocellular Carcinoma



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### **H&O** Which hepatocellular carcinoma patients benefit from sorafenib monotherapy?

**JC** Sorafenib (Nexavar, Bayer HealthCare) is the only systemically applicable drug able to prolong survival, though only modestly, in patients with advanced-stage hepatocellular carcinoma (HCC) if used as a monotherapy. This was established by 2 randomized, placebo-controlled clinical trials: SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) and AP (Asia-Pacific). Thus, sorafenib was approved by the US Food and Drug Administration for monotherapy use in HCC patients categorized as Barcelona Clinic Liver Cancer (BCLC) stage C, many of whom have locally advanced disease with macrovascular invasion or extrahepatic metastases.

In practice, however, there is a growing tendency to treat a number of those BCLC stage C patients with image-guided locoregional therapies, such as transarterial chemoembolization (TACE), either alone or in combination with sorafenib. These therapies have been proven to be safe, and there are some data in support of equal or even better survival outcomes after intra-arterial therapies with or without combined sorafenib as compared with sorafenib alone.

### **H&O** When is TACE traditionally indicated for HCC, and how effective is it?

**JC** The practical indication and use of TACE have gone far beyond what was initially supported by the guidelines and staging systems such as BCLC. Clinically, TACE is

now being used not only in intermediate-stage HCC (ie, BCLC stage B), but also for downstaging purposes prior to surgery or as a bridge to liver transplant in patients with early-stage disease.

As previously mentioned, TACE can also be used for patients with advanced-stage disease and, in fact, can be more effective than sorafenib alone. This has been recognized and implemented within the recently introduced Hong Kong Liver Cancer Staging System. This system allows patients with limited macrovascular invasion, specifically those with branch portal vein invasion or asymptomatic extrahepatic disease, to also be treated with TACE.

Overall, the data are quite clear on the ability of TACE to achieve a complete or near-complete tumor kill and to significantly prolong survival. In fact, much of the data on the use of TACE in patients with intermediate-stage HCC report a median survival of 26 to 27 months.

### **H&O** What is the rationale for combining sorafenib and TACE for the treatment of HCC?

**JFG** The rationale for this combination is based on science. We have known for some time that chemoembolization causes hypoxia within the tumor that in turn leads to stimulation of angiogenesis, which promotes tumor survival and growth and is the leading cause of incomplete tumor kill. It also leads to tumor recurrence. Therefore, using a drug with strong antiangiogenic properties, such as sorafenib, in combination with TACE could potentiate the effects of TACE. As such, sorafenib is likely to mitigate the proangiogenic effects of TACE, thereby reducing the

chance of recurrence. Thus, combining a drug that has antiangiogenic properties with TACE, which has proangiogenic effects, is very appealing.

The potential benefit of combining sorafenib and TACE prompted the initiation of several clinical trials. Although the safety profile has now been clearly established, the efficacy remains unknown. Recent papers suggest a clinical benefit with the combination, but definitive studies have not yet confirmed this.

### **H&O** What observations have been reported from the GIDEON registry regarding the combination of sorafenib and TACE?

**JFG** The GIDEON (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of Treatment With Sorafenib) registry is a prospective, observational study of more than 3000 HCC patients that was compiled by researchers throughout the world, including myself. This is the largest phase 4 observational registry of patients treated with sorafenib. Entry into the study began with initiation of sorafenib therapy.

My colleagues and I noted 2 interesting observations from this registry regarding the combined use of TACE and sorafenib. The first involved patients who were pretreated with TACE before enrolling in GIDEON. These patients did much better than patients who did not receive TACE before starting sorafenib. The second interesting observation was that patients who received TACE and sorafenib concomitantly did much better than patients who received these treatments separately. These observations may very well be explained both by the beneficial effects of TACE on overall survival as well as by the fact that patients who demonstrated disease progression after embolotherapy may have experienced a surge of proangiogenic factors after TACE and thus benefited from sorafenib the most.

### **H&O** How do these GIDEON observations compare with findings from other studies?

**JFG** The GIDEON data support the findings that have been reported by others—that patients with more advanced HCC (those with portal vein invasion and extrahepatic disease) who were on sorafenib as recommended by current clinical guidelines, in addition to TACE, did better than those patients who received either therapy alone.

### **H&O** What have other studies reported regarding this combination?

**JC** There have been many single-center and multicenter studies looking at the combination of TACE and

sorafenib. Dr Geschwind and colleagues conducted a study that was started at The Johns Hopkins University School of Medicine, in which patients with limited macrovascular invasion and asymptomatic extrahepatic disease did very well with the combination of sorafenib and TACE. The recently published final results from the START (Study in Asia of the Combination of TACE With Sorafenib in HCC Patients) trial supported those findings and demonstrated that combining TACE and sorafenib is well tolerated and effective. In another study, researchers from Seoul National Cancer Center also demonstrated that concurrent TACE with sorafenib demonstrated a manageable safety and toxicity profile, which is clearly the case from the experience of our group.

### **H&O** Should the negative results of some combination trials, such as the SPACE trial, cause concern?

**JFG** There have been several trials on this combination that have had negative results, such as the SPACE (Sorafenib or Placebo in Combination With Transarterial Chemoembolization for Intermediate-Stage Hepatocellular Carcinoma) trial, which examined the use of drug-eluting bead TACE with or without sorafenib in patients with intermediate-stage HCC. However, I think that the SPACE trial tested this combination in the wrong patient population because the trial was designed to enroll only BCLC stage B patients. I am convinced—and the recent data support this—that the results would have been much more favorable with the combination of TACE and sorafenib had patients with BCLC stage C been included. Our data clearly show that patients with limited portal vein invasion who were able to tolerate sorafenib for at least 6 months and were treated with TACE throughout sorafenib therapy did much better in terms of survival than those who were unable to tolerate sorafenib for more than 2 months or so. It therefore seems that the combination of TACE and sorafenib should be reserved for patients with advanced, unresectable HCC.

### **H&O** Does the addition of sorafenib increase toxicity? What studies have been conducted on the safety of this combination?

**JFG** As already mentioned, the combination of TACE and sorafenib is safe even when given concurrently. The findings have been very supportive; the data show no additional toxicity as a result of the addition of sorafenib. My colleagues and I conducted the initial US study on the combination, with a primary endpoint of toxicity. We found that simultaneous administration of sorafenib and TACE throughout all TACE treatment sessions was

safe and that the combination was effective as long as the patients continued receiving sorafenib for at least 6 months.

**H&O** Should this combination be avoided in any patients with advanced HCC?

**JFG** The combination should be avoided in any patients who should not receive either TACE or sorafenib alone. In other words, the toxicity profile of the combination is the same as that of either therapy alone.

**H&O** Does the dosage of sorafenib need to be adjusted when combined with TACE?

**JFG** I am not sure that data recommend adjusting the dose of sorafenib if the patient is already on TACE. In the SHARP and AP studies, the vast majority of patients did require dose adjustment, particularly dose reduction. However, these patients were on sorafenib monotherapy, so the dose adjustment had nothing to do with combination therapy. It is also noteworthy that the GIDEON data have shown that dose adjustment is common in clinical practice throughout the world.

**H&O** Does the use of a particular type of TACE or the number of treatments affect patient outcomes?

**JFG** There is no way to extract that information from the data currently available. For example, several of the trials with TACE were performed with drug-eluting beads and several with other types of TACE, so it is not possible to determine whether one is better than the other. However, when contemplating the use of TACE in combination with sorafenib, it makes sense to use conventional TACE rather than TACE with drug-eluting beads because conventional TACE is the gold standard.

**H&O** Does the sequence of administering TACE and sorafenib affect outcomes?

**JFG** Again, there are currently no data to directly compare different sequences of administration. We do know that the safety profile of the combination does not change whether sorafenib is administered sequentially, is interrupted, or is administered continuously. That being said, I feel that continuous administration of sorafenib

throughout the planned cycles of chemoembolization is the best option because sorafenib is being used the entire time and the patient is not being deprived of any potential benefit of the drug.

**H&O** Do you know of any upcoming or ongoing studies examining this combination?

**JFG** My colleagues and I at the Yale School of Medicine are hoping to perform a randomized trial of TACE plus sorafenib administered continuously vs sequentially to determine whether there is a difference in outcomes between the 2 options.

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**Suggested Reading**

Chao Y, Chung YH, Han G, et al. The combination of transcatheter arterial chemoembolization and sorafenib is well tolerated and effective in Asian patients with hepatocellular carcinoma: final results of the START trial. *Int J Cancer*. 2015;136(6):1458-1467.

Chapiro J, Duran R, Geschwind JF. Combination of intra-arterial therapies and sorafenib: is there a clinical benefit? *Radiol Med*. 2014;119(7):476-482.

Cheng AL, Amarapurkar D, Chao Y, et al. Re-evaluating transarterial chemoembolization for the treatment of hepatocellular carcinoma: consensus recommendations and review by an International Expert Panel. *Liver Int*. 2014;34(2):174-183.

Cosgrove DP, Reyes DK, Pawlik TM, Feng AL, Kamel IR, Geschwind JF. Open-label single-arm phase II trial of sorafenib therapy with drug-eluting bead transarterial chemoembolization in patients with unresectable hepatocellular carcinoma: clinical results. *Radiology*. 2015;277(2):594-603.

Geschwind JF, Gholam PM, Goldenberg A, et al. Use of transarterial chemoembolization (TACE) and sorafenib in patients with unresectable hepatocellular carcinoma: US regional analysis of the GIDEON registry. *Liver Cancer*. 2016;5(1):37-46.

Geschwind JF, Kudo M, Marrero JA, et al. TACE treatment in patients with sorafenib-treated unresectable hepatocellular carcinoma in clinical practice: final analysis of GIDEON. *Radiology*. 2016;279(2):630-640.

Park JW, Amarapurkar D, Chao Y, et al. Consensus recommendations and review by an International Expert Panel on Interventions in Hepatocellular Carcinoma (EPOIHCC). *Liver Int*. 2013;33(3):327-337.

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