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 intraarterial 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 pro-
angiogenic 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 Hepato-
cellular 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**


