INTERVIEW

Bert H O'Neil, MD

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Tracks 1-12

Track 1 **Case 5 discussion:** A 68-year-old man with HCV-related, recurrent HCC after liver transplant 8 years ago undergoes chemoembolization

Track 2 Chemoembolization with or without sorafenib in unresectable HCC

Track 3 Side effects, dose reduction and supportive care measures with sorafenib

Track 4 Evaluation of novel agents in advanced HCC

Track 5 **Case 6 discussion:** A 55-year-old man with a 5-cm, HCV-related HCC and Child-Pugh B liver disease

Track 6 **Case 7 discussion:** A 58-year-old man who has HCV-related HCC with portal vein thrombosis, thrombocytopenia and Child-Pugh A liver disease

Track 7 Use of yttrium-90 microspheres for patients with advanced HCC and portal vein thrombosis

Track 8 Perspective on the benefits of locoregional versus systemic therapy for advanced HCC

Track 9 Use of sorafenib among medical oncologists and hepatologists for HCC

Track 10 Capecitabine-based chemoradiation therapy for the preoperative treatment of rectal cancer

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Track 12 Investigation of dual antibody therapy for patients with K-ras wild-type mCRC

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What criteria do you consider to determine which patients with HCC are appropriate for transplant as opposed to resection?

DR O'NEIL: Resection is not an option for patients with severe cirrhosis, even in those with small tumors. However, these patients may fall within the UNOS criteria for transplant — having either 1 lesion of 5 centimeters or less or 3 or fewer lesions of less than 3 centimeters in diameter. The long-term survival rate after transplant for patients with those criteria is about 80%, so it's quite an effective therapy.

By contrast, for a similar patient who is a candidate for resection, you're probably looking at more like a 40% to 50% long-term survival rate because of worsening of liver disease or development of new tumors elsewhere in the liver.

DR LOVE: For which patients do you consider local therapy as a bridge to transplant?

DR O'NEIL: For patients with borderline tumors — ie, those between 3½ and just smaller than 5 centimeters — we will often consider this approach. The procedure we prefer at our institution is embolization because it has good response rates. It allows the patient to stay on the transplant list without experiencing progression, and I believe it's a good way to care for that particular group of patients. Another option for some patients is ablation, although some concerns persist about tracked seeding when you perform ablation.

DR LOVE: What are your thoughts on the integration of sorafenib with chemoembolization?

DR O'NEIL: The answer to that question will come from the ECOG-E1208 study in which patients with unresectable HCC receive sorafenib prior to transarterial chemoembolization (TACE). Sorafenib is discontinued for a few days around the procedure but then resumed and continued until progression (2.1).

DR LOVE: Do you believe this strategy is reasonable outside a protocol setting?

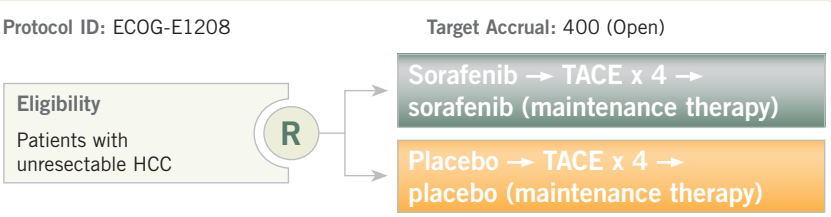
DR O'NEIL: That is a tough question. We perform embolization for different types of patients. One is the group of patients with unresectable tumors, such as tumors that are too large to ablate but are quite vascular. Some of those patients fare remarkably well with embolization. Some of my patients have undergone repeated embolizations for a number of years. I find it hard to imagine that such a patient would benefit much from concomitant sorafenib.

But some patients clearly don't respond well to embolization, and they end up receiving sorafenib relatively shortly thereafter. So you wonder if starting the sorafenib earlier, around the time of embolization, might benefit those patients.

Additionally, data suggest that when we perform an embolization, the tumor secretes VEGF in response to the hypoxia. Perhaps that might assist the

2.1

Phase III Study of Transarterial Chemoembolization (TACE) with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC)

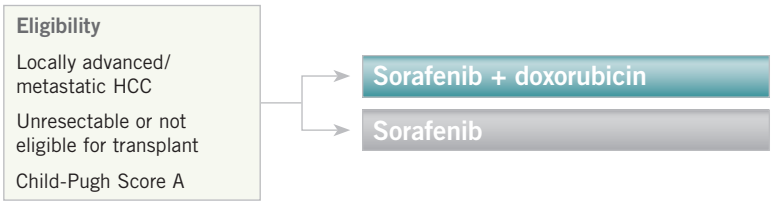


www.clinicaltrials.gov, October 2011.

2.2

Randomized Phase III Study Comparing Sorafenib and Doxorubicin to Sorafenib Alone in Locally Advanced or Metastatic Hepatocellular Carcinoma (HCC)

Protocol ID: CALGB-80802 **Target Accrual:** 480 (Open)



www.clinicaltrials.gov, October 2011.

tumor's growth in the postembolization period, and maybe inhibiting VEGF signaling with sorafenib around the time of embolization might help. I believe we need more randomized data before we routinely adopt such an approach.

Track 4

DR LOVE: Are there any new encouraging research strategies in HCC?

DR O'NEIL: The CALGB has an interesting study evaluating the combination of doxorubicin and sorafenib (2.2) based on some Phase II data on this combination (Abou-Alfa 2010; [2.3]). Some people have limited enthusiasm for doxorubicin, given that it is an older agent and is a bit toxic, but I believe this is an important study that needs to be done.

2.3

Sorafenib and Doxorubicin (S + D) versus Placebo and Doxorubicin (P + D) for Advanced Hepatocellular Carcinoma

	S + D (n = 47)	P + D (n = 49)	Hazard ratio	*p*-value
Median time to progression	6.4 months	2.8 months	0.50	0.02
Median overall survival	13.7 months	6.5 months	0.49	0.006
Median progression-free survival	6.0 months	2.7 months	0.54	0.006

Abou-Alfa GK et al. *JAMA* 2010;304(19):2154–60.

Tracks 6-8

Case discussion

A 58-year-old man who has HCV-related HCC with portal vein thrombosis (PVT), thrombocytopenia and Child-Pugh A liver disease.

DR O'NEIL: This patient would have been a candidate for the SHARP trial evaluating sorafenib in HCC (Llovet 2008). For someone like him, the question right from the outset was, is it better to use regional therapy or start the patient on sorafenib, or should we do both? Without the data, I'm hesitant to do both.

This is one of those borderline areas in which little consensus is seen regarding the best treatment approach. We have several strategies for this type of patient. The patient was not eligible for transplant. His spleen was fairly large and his platelet count was about 38,000, so we were unable to perform a resection and were stuck with this localized but effectively incurable tumor.

This patient received treatment with yttrium-90 microspheres (Y-90). Y-90 is used quite a bit without any randomized data. A large case series study has shown an improvement in overall survival with Y-90 versus a regional therapy (Carr 2010), but no randomized data have been presented against any other form of therapy. One advantage of Y-90 is that it is safer to administer in the setting of PVT than chemoembolization. The reason is that although these are embolic particles, the number of particles in a treatment is designed to deliver a particular radiation dose but does not fully embolize the region.

With chemoembolization, if you have an issue with the portal vein and you embolize the artery, you effectively have no blood flow to that segment of the liver, which can result in complications. In bad cases, patients can experience complete necrosis of an area. They'll experience hepatocyte damage in that region, and some patients don't have enough liver reserve to tolerate that. This can result in liver failure. Chemoembolization can be performed. It's not an absolute contraindication. With the improved catheters of today, you can get to smaller portions of the liver. But most of us still consider a major PVT to be at least a relative contraindication to chemoembolization.

This patient's tumor was hard to measure, so we followed him for a few months with MRI. He had stable disease for quite some time but then eventually developed venous thrombosis and evidence of tumor involvement in the opposing lobe. This posed a dilemma: Do we keep chasing this with regional therapy or move to systemic therapy? My preference is to move to sorafenib in such cases, and he has now been receiving sorafenib for about 6 months. Because of the diffuse nature of the patient's tumor, we didn't expect to see much change. Portal vein thrombi tend to remain static. So in his case we're looking for lack of disease progression as a sign of benefit. He's tolerated sorafenib well with only minor hand-foot issues, for which we paused therapy without dose reduction. ■

SELECT PUBLICATIONS

Abou-Alfa GK et al. **Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: A randomized trial.** *JAMA* 2010;304(19):2154-60.

Carr BI et al. **Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: A two-cohort study.** *Cancer* 2010;116(5):1305-14.

Llovet JM et al. **Sorafenib in advanced hepatocellular carcinoma.** *N Engl J Med* 2008;359(4):378-90.