INTERVIEW

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CD 2, Tracks 6-12

Track 6 Critical assessment of local treatment modalities in hepatocellular carcinoma (HCC): Resection, transplantation or radiofrequency ablation

Track 7 Therapeutic interventional strategies based on differential blood flow of HCC versus normal liver

Track 8 TACE with or without sorafenib for patients with HCC and extrahepatic metastases

Track 9 Identification of patients with advanced Child-Pugh B HCC who may benefit from sorafenib

Track 10 Evaluation of performance status, hepatic function and age when considering initial and subsequent dosing of sorafenib for patients with advanced HCC

Track 11 Management of sorafenib-associated hand-foot syndrome

Track 12 Heterogeneity of biliary tract cancers and opportunities for development of novel treatments

Select Excerpts from the Interview

CD 2, Track 6

DR LOVE: What curative treatment modalities should a physician consider when evaluating a patient with newly diagnosed hepatocellular carcinoma (HCC)?

DR ZHU: The key options that a medical oncologist should carefully assess when first evaluating a patient with HCC are surgical resection, liver transplant or local ablative therapy, particularly radiofrequency ablation, which can be curative in this setting.

If you diagnose HCC at an early stage, outcomes are overwhelmingly good, within the neighborhood of 70% to 80% survival at 5 years. This is in contrast to some of the aggressive tumors that we as GI medical oncologists deal with, for example, pancreatic cancer. Therefore, I always make a strong point to evaluate patients with HCC for definitive treatment.

CD 2, Tracks 9-11

DR LOVE: Would you discuss the role of systemic therapies like sorafenib for patients with HCC who have Child-Pugh B and Child-Pugh C disease?

DR ZHU: A large number of patients with HCC present with underlying Child-Pugh B or C cirrhosis. Patients with Child-Pugh C disease should not receive systemic

therapies such as sorafenib. The best option for these patients with severe underlying cirrhosis is careful follow-up with a hepatologist. Cirrhosis-related complications need to be appropriately managed to ensure the control of ascites and to prevent encephalopathy and severe upper GI bleeding.

It's important to consider that not all Child-Pugh B disease is the same. The Child-Pugh classification is a rough estimate of the underlying hepatic function. But we know from extensive clinical experience that sorafenib can be safely administered to patients with Child-Pugh B disease, particularly if they have a B7 Barcelona Clinic Liver Cancer staging score. When sorafenib is administered to this population, duration of treatment and time to tumor progression are shorter compared to the benefits exhibited in patients with Child-Pugh A disease. Although patients with Child-Pugh B disease derive some benefit with sorafenib, the duration of benefit tends to be shorter.

DR LOVE: What dosing regimen of sorafenib do you follow for patients with HCC?

DR ZHU: The dose of sorafenib in patients with HCC remains controversial. Two pivotal Phase III studies, the SHARP trial and another study conducted in the Asian-Pacific region, evaluated the 400-mg dose twice daily and demonstrated that sorafenib improved overall survival compared to placebo (Llovet 2008; Cheng 2009).

Many community oncologists administer half that dose, either 200 mg twice daily or 400 mg daily (Venook 2011). If patients tolerate the drug at a reduced dose, then it can be gradually escalated to the full dose. I only use that strategy for patients with borderline performance status or those with Child-Pugh B disease. This avoids some of the toxicities associated with sorafenib that could potentially lead to its discontinuation. If the patient is young, has a good performance status and has compensated hepatic function, the standard 400-mg, twice-daily dose can be administered.

Currently we have no data to determine which dosing regimen is better tolerated and would lead to a longer time on treatment or time-to-tumor progression. I suggest that community oncologists assess the patient's performance status and the underlying hepatic function to determine the dosing regimen for sorafenib.

DR LOVE: Would you recommend the full dose of sorafenib for an elderly patient who has a robust performance status and good liver function?

DR ZHU: I would not discriminate based on the patient's age alone. I would use my earlier criteria and would consider the full dose if the patient's performance status was robust.

DR LOVE: What are your thoughts on the recent ASCO presentation (Ren 2012; [3.1]) on the use of a urea-based cream to treat the hand-foot skin reaction associated with sorafenib in patients with advanced HCC?

DR ZHU: Many strategies have been employed to manage sorafenib-associated skin toxicity. We have used the urea-containing cream in our practice. This study definitely has its merits, but I don't believe that the open-label study design was the best approach to determine whether a urea-based cream could decrease the skin toxicity associated with sorafenib. We need additional studies to definitively address this issue.

DR LOVE: Do you use any strategies preemptively to prevent hand-foot skin reaction?

DR ZHU: I always encourage patients to moisturize their skin carefully. Particular attention should be given to the palms of the hands and soles of the feet because the hand-

foot skin reaction tends to occur early and with more severity in those areas. Beyond that I do not currently use pharmacological intervention as a preventive strategy for the hand-foot syndrome associated with sorafenib. ■

3.1

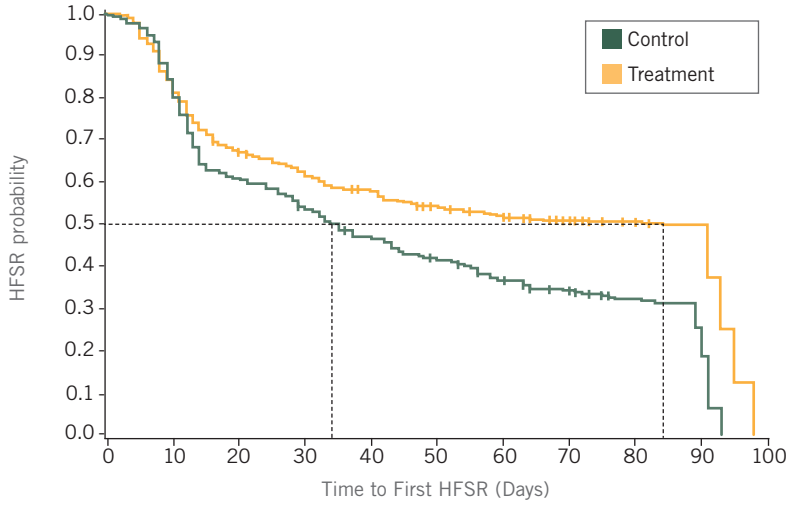
Randomized Phase II Study of the Prophylactic Effect of Urea-Based Cream on the Hand-Foot Skin Reaction (HFSR) Associated with Sorafenib in Advanced Hepatocellular Carcinoma

Primary endpoint: Incidence of all-grade HFSR

Grade of HFSR	Urea cream + BSC (n = 439)	BSC (n = 432)	*p*-value
All grades	56.0%	73.6%	<0.0001
Grade 2 or 3	20.7%	29.2%	0.004

Secondary endpoints include time to first HFSR event

The median time to first HFSR event was 2.5 times as long in the urea cream + BSC arm (n = 354) as in the BSC arm (n = 345) (84 days versus 34 days; $p < 0.0001$).



BSC = best supportive care

With permission from Ren Z et al. *Proc ASCO* 2012;**Abstract 4008**.

SELECT PUBLICATIONS

Cheng A et al. **Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial.** *Lancet Oncol* 2009;10(1):25-34.

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

Ren Z et al. **A randomized controlled phase II study of the prophylactic effect of urea-based cream on the hand-foot skin reaction associated with sorafenib in advanced hepatocellular carcinoma.** *Proc ASCO* 2012;**Abstract 4008**.

Venook A et al. **First interim results of the global investigation of therapeutic decisions in hepatocellular carcinoma (HCC) and of its treatment with sorafenib (GIDEON) study: Use of sorafenib (Sor) by oncologists and nononcologists in the management of HCC.** Gastrointestinal Cancers Symposium 2011;**Abstract 157**.