



Sorafenib plus doxorubicin in advanced hepatocellular carcinoma patients: hope or hype?

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More than a decade ago, sorafenib changed the treatment landscape of advanced hepatocellular carcinoma (HCC) by showing an overall survival (OS) benefit compared with placebo (1). The reported median 2.8-month OS benefit was encouraging, but low response rates and the lack of predictive biomarkers meant that significant clinical benefit remains limited and confined to patients with preserved liver function. Since a fraction of HCC are chemo-sensitive, investigators have attempted to combine chemotherapy with sorafenib to enhance treatment efficacy. Doxorubicin and sorafenib was tolerable and safe at dose finding, and have been tested in a phase 3 randomized controlled trial by Abou-Alfa *et al.* (2,3). This study compares the combination with sorafenib to address important questions regarding efficacy and safety.

The multicentered alliance-led study randomized 356 untreated patients with histologically proven advanced HCC at 1:1 ratio to sorafenib and doxorubicin (n=180) *vs.* sorafenib alone (n=176). With a target recruitment of 480 patients, the study was prematurely terminated in 2015 for futility at interim analysis. It had stringent criteria for study entry: including an Eastern Cooperative Oncology Group performance status of 0–1, Child-Pugh Class A liver function, adequate hematological parameters, and adequate left ventricular systolic function defined as 45% and above.

Baseline characteristics were similar between the study arms with approximately 58% and 57% contributed by metastatic disease in the respective arms. Most patients were Caucasian (67%), explaining the low rates of hepatitis B (8.9% and 9.7% respectively) as compared with hepatitis C etiology (21% and 18%). However, the hepatitis status of 167 patients,

45% of the doxorubicin plus sorafenib arm and 48.9% of the sorafenib arm, nearly half of the study population, were unknown. Sorafenib was given at 400 mg twice daily for both arms while doxorubicin was dosed at 60 mg/m² every 3 weeks up to an accumulative dose of 360 mg/m². Median dose of doxorubicin was 237.5 mg (range, 0–1,036 mg) over a median of 3 cycles, while median sorafenib doses were 433 mg (range, 19–895 mg) and 495 mg (range, 38–994 mg) respectively. The primary endpoint of median OS was 9.3 months (95% CI, 7.3–10.8 months) for sorafenib plus doxorubicin and 9.4 months (95% CI, 7.3–12.9 months) for sorafenib alone (hazard ratio, 1.05; 95% CI, 0.83–1.31). Progression free survival was likewise no different between the study arms (median 4.0 *vs.* 3.7 months; hazard ratio, 0.93; 95% CI, 0.75–1.16).

This study reiterates the marginal benefit of chemotherapy in HCC and confirms the lack of clinical benefit over sorafenib when given in combination (2,4). Numerous chemo-resistant mechanisms in HCC have been documented: including recurrent TP53 mutations and P-glycoprotein expression (5,6). Further, treatment of human HCC cell lines with doxorubicin led to the rapid emergence of resistant clones which upregulate P-glycoprotein and epithelial-to-mesenchymal marker SNAIL (7). Consistently, adding doxorubicin did not increase response rates (P=0.52), but increased rates of grade 3–4 neutropenia (36.8%) and thrombocytopenia (17.5%). These toxicities likely contributed to cycle delays, dose reductions, and compromised efficacy. Clinically relevant adverse events related to doxorubicin in this population of background liver disease such as infection,

neutropenic fever, bleeding, and hepatic decompensation were not reported. Antiviral medication was also not reported for hepatitis B patients. Grade 3–4 cardiac toxicity and decreases in left ventricular ejection fraction occurred in 3.0% and 4.8% of patients on doxorubicin respectively, raising questions regarding the safety and tolerability of this combination.

Recently, next generation kinase inhibitors and immune checkpoint inhibitors have shown efficacy in HCC (8,9). These studies not only address later line treatment options after sorafenib, but in the case of immune checkpoint blockade, have charted new treatment opportunities for patients with more advanced liver disease that are contraindicated for multi-kinase inhibitors. Although the current trial has failed to demonstrate benefit with the addition of doxorubicin to sorafenib, studies of cytotoxic-chemotherapy and anti-PD-1 combinations may still be of relevance to immunogenic cell death and potentiation of anti-tumor immunity (10).

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