Combination therapy improves survival time for patients with advanced liver cancer

November 16 2010

Treatment of inoperable advanced liver cancer with the agent doxorubicin (routinely used to treat this condition) in addition to the agent sorafenib resulted in greater overall survival and progression-free survival, compared to patients who received treatment with doxorubicin alone, according to a study in the November 17 issue of *JAMA*.

"Hepatocellular [liver] carcinoma (HCC) is the sixth most common malignancy worldwide, with approximately 600,000 new cases per year. Patients with inoperable or metastatic disease have a median [midpoint] survival of only a few months. Despite the lack of a clear survival benefit, doxorubicin has become a routinely and widely used agent in the treatment of HCC," according to background information in the article. Sorafenib has shown a statistically significant increase in median overall survival compared to placebo. A phase 1 study assessing the feasibility and tolerability of sorafenib in combination with doxorubicin for patients with solid tumors has shown promise. The combination of sorafenib and doxorubicin in patients with advanced HCC has not been evaluated in a phase 2 or 3 trial.

Ghassan K. Abou-Alfa, M.D., of Memorial Sloan-Kettering Cancer Center, New York, and colleagues conducted a randomized, phase 2 study of doxorubicin plus sorafenib and doxorubicin plus placebo in patients with advanced HCC. The study, conducted from April 2005 to October 2006, included 96 patients (76 percent male; median age, 65 years) who were randomly assigned to receive doxorubicin intravenously every 21 days plus either sorafenib or placebo orally twice a day. The

date of the last patient's follow-up was April 2008.

Following complete accrual, an unplanned early analysis for efficacy was performed by the independent data monitoring committee, so the trial was halted. The 2 patients remaining in the placebo group at that time were offered sorafenib.

There were 51 total time-to-disease progression events (24, doxorubicin plus sorafenib vs. 27, doxorubicin plus placebo). Time to disease progression was a median of 6.4 months for patients who received doxorubicin plus sorafenib and 2.8 months for those who received doxorubicin plus placebo.

Sixty-three patients died during the course of the study: 25 in the doxorubicin-sorafenib group; 38 in the doxorubicin-placebo group. Median overall survival was 13.7 months among patients treated with doxorubicin plus sorafenib vs. 6.5 months among those who received doxorubicin plus placebo. Analysis indicated a 51 percent reduction in the risk of death in patients treated with doxorubicin and sorafenib vs. doxorubicin and placebo.

The number of total progression-free survival events was 70, including 32 in the doxorubicin-sorafenib group and 38 in the doxorubicin-placebo group, with the median progression-free survival being 6 months among patients treated with doxorubicin plus sorafenib vs. 2.7 months among those who received doxorubicin plus placebo. Analysis showed a 46 percent reduction in the risk of progression or death among patients treated with doxorubicin plus sorafenib vs. doxorubicin plus placebo.

Toxicity profiles were similar to those for the single agents.

"In summary, among patients with advanced HCC, treatment with sorafenib doxorubicin compared with doxorubicin plus placebo resulted

in greater median time to progression, overall survival, and progression-free survival. The degree to which this improvement may represent synergism between sorafenib and doxorubicin remains to be defined. This trial has served as the basis for the ongoing phase 3 trial of sorafenib plus doxorubicin vs. sorafenib alone," the authors conclude.

More information: *JAMA*. 2010;304[19]:2154-2160.