TARGETED THERAPIES

Doxorubicin and sorafenib improves survival in patients with advanced hepatocellular carcinoma

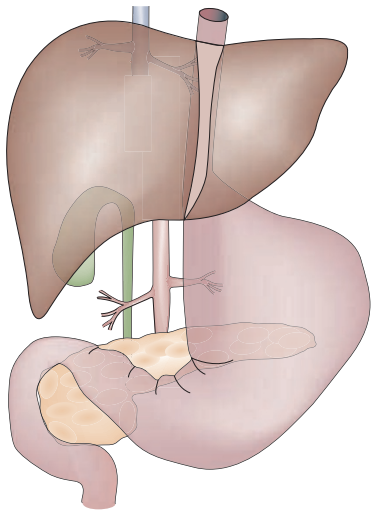
Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide and over half a million cases are diagnosed annually. The prognosis for patients with unresectable or metastatic disease is dismal with most patients only surviving a few months following diagnosis. Doxorubicin has become a routinely used agent for the treatment of HCC, despite no evidence of a clear survival benefit. In a randomized, double-blinded, phase III trial of patients with advanced HCC and Child–Pugh A cirrhosis, the oral multikinase inhibitor, sorafenib, has demonstrated a significant overall survival advantage. Thus, the feasibility and tolerability of the combination of sorafenib and doxorubicin was tested in a phase I study. In this study, the combination of 60 mg/m^2 doxorubicin and 400 mg sorafenib was well tolerated in patients with refractory disease. This finding prompted the testing of this combination in a phase II study in patients with advanced HCC, as Abou-Alfa, the lead investigator of the trial comments, "randomized phase II studies are favorable as they help understand better the outcome of a certain therapy in comparison to historical controls and can help identify a potential winner to be studied further in a phase III study".

Abou-Alfa and coauthors assessed the efficacy and safety of doxorubicin combined with sorafenib compared with doxorubicin alone in patients with Child–Pugh A and advanced HCC. In this double-blinded, multinational, phase II study, 96 patients with histologically proven inoperable HCC who had received no previous treatment were enrolled to the study from 25 centers. Patients received 60 mg/m^2 of doxorubicin intravenously every 21 days until the maximum total dose reached was 360 mg/m^2 and either 400 mg sorafenib (n = 47) or placebo (n = 49) orally twice daily. The median time to progression for patients receiving sorafenib was 6.4 months and for those in the placebo arm it was 2.8 months. The median overall survival was significantly improved in patients receiving sorafenib (13.7 months) compared to those receiving doxorubicin alone (6.5 months), which represented a 51% reduction in the risk of death for the sorafenib treated patients.

The total number of progression-free survival events was 70, of which 32 occurred in the doxorubicin and sorafenib group and 38 in the placebo group. The median progression-free survival was 6 months for patients treated with sorafenib compared with only 2.7 months for those receiving doxorubicin alone. This outcome represents a 46% reduction in the risk of progression or death in patients treated with the sorafenib and doxorubicin combination. Radiologic response rate assessment revealed that tumor shrinkage occurred in a considerably greater number of patients receiving sorafenib and doxorubicin (62%) compared with those treated with doxorubicin alone (29%).

The toxic effects profile for patients in the combination arm was similar to those reported for the single agents and was as expected for both agents. Grade 3 and 4 toxic effects included fatigue, hand and foot reaction, diarrhea, and neutropenia. All-grade left-ventricular systolic dysfunction was noted in 19% of patients receiving sorafenib and doxorubicin and 2% of those in the control arm. All-grade hypertension was reported for 8 patients receiving sorafenib and doxorubicin and none for those receiving doxorubicin alone.

Owing to the reported survival advantage for sorafenib-treated patients in the interim results of a phase III trial of sorafenib versus placebo, an unplanned interim analysis for efficacy was performed. While these interim results were immature, because the patients randomized to receive doxorubicin and placebo were at a considerable disadvantage compared to those treated with the sorafenib and doxorubicin combination, the trial was discontinued and patients were unblinded, so that the two patients who remained in the placebo arm could be offered sorafenib.



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The investigators also noted: "the lack of a comparative sorafenib standard group in our trial precludes any assessment of potential synergism between doxorubicin and sorafenib. Thus, whether doxorubicin contributed significantly to the outcome or whether the benefit seen in the doxorubicin–sorafenib group was the result of sorafenib alone, cannot be determined from the results of this trial".

As Abou-Alfa notes, "improvement in time to progression, progression-free survival and overall survival compares favorably to the standard of care of sorafenib as a single agent". Owing to the positive results of this study this "has served as the basis for the ongoing phase III trial of sorafenib plus doxorubicin versus sorafenib alone". The results of this trial are eagerly awaited.

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