Sorafenib in Hepatopulmonary Syndrome (SHPS): A Randomized, Double-Blind Placebo-Controlled Trial

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Introduction: The tyrosine kinase inhibitor sorafenib improves hepatopulmonary syndrome (HPS) in an experimental model. However, the efficacy and side effect profile in patients with HPS are unknown. We aimed to determine the effect of sorafenib on the alveolar-arterial oxygen gradient ($AaPO_2$) at three months in patients with HPS.

Methods: We performed a randomized, double-blind, placebo-controlled parallel trial of sorafenib in patients with HPS at seven centers. A total of 28 patients with HPS were randomized to sorafenib 400 mg by mouth daily or matching placebo in a 1:1 ratio.

Results: We found no statistically significant difference in the change in $AaPO_2$ from baseline to 12 weeks between the patients allocated to sorafenib (median [interquartile range] +4.5 mm Hg [-3.8-7.0]) and those allocated to placebo (-2.4 mm Hg [-4.8-8.2]) ($p = 0.70$). There was also no difference between the groups in terms of degree of intrapulmonary shunting by contrast echocardiography. Sorafenib significantly reduced circulating levels of angiogenic markers, including vascular endothelial growth factor receptors ($p < 0.01$) and Tie2-expressing M2 monocytes ($p = 0.03$), but also lowered the mental component scores of the Short Form-36 ($p = 0.04$), indicating worsening quality of life.

Conclusion: Sorafenib did not change the $AaPO_2$ or other disease markers at three months in patients with HPS. Alternative anti-angiogenic therapies or treatments targeting other pathways should be investigated.

Clinical Trial Registration: clinicaltrials.gov, NCT02021929

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