Intern Med 2017, 7:4 (Suppl)
DOI: 10.4172/2165-8048-C1-006

The role of cyproheptadine in the treatment of hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is a major cause of cancer deaths worldwide. However, current chemotherapeutic drugs for advanced stage HCC are either poorly effective or expensive, and treatment with these drugs has not led to satisfactory outcomes. In a BMJ 2012 case report, we described our breakthrough finding in two advanced HCC patients, one of whom achieved complete remission of liver tumors and the other a normalized -fetoprotein level, along with complete remission of their lung metastases, after the concomitant use of thalidomide and cyproheptadine. We assumed the key factor in our effective therapy to be cyproheptadine in light of a previous finding that cyproheptadine affects the cell cycle and impedes leukemia cell growth by inhibiting transcription factors involved in the expression of D-cyclins. We investigated the antiproliferative effects of cyproheptadine, as well as the molecular mechanisms, which were involved in two human HCC cell lines: HepG2 and Huh-7. We identified that cyproheptadine has a potent inhibitory effect on the proliferation of HepG2 and Huh-7 cells but minimal toxicity in normal hepatocytes. Additionally, cyproheptadine elevated the percentage of Huh-7 cells in the sub-G1 population and raised the levels of PARP and its cleaved form, indicating induction of apoptosis. Finally, cyproheptadine-mediated cell cycle arrest was dependent upon the activation of p38 MAP kinase in HepG2 cells and the activation of both p38 MAP kinase and CHK2 in Huh-7 cells. Our results demonstrated that the non-classical p38 MAP kinase function of regulation of cell cycle checkpoints is one of the underlying mechanisms promoted by cyproheptadine to suppress the proliferation of HCC cells, and provide evidence for the drug's potential as a treatment option for liver cancer. In the clinical aspect, we evaluate the efficacy of sorafenib plus cyproheptadine compared with sorafenib alone in patients with advanced hepatocellular carcinoma. A retrospective cohort study, published in JJCO 2015, reviewed all consecutive advanced hepatocellularcarcinoma cases with Child-Pugh Class A disease starting sorafenib treatment at our hospital from August 2012 to March 2013.They were followed up until 31December 2013. A total of 52 patients were enrolled: 32 patients in the combination (sorafenib–cyproheptadine) group and 20 patients in the control (sorafenib alone) group. The response to treatment, overall survival and progression-free survival were compared. The results showed : The median overall survival was 11.0 months in the combination group compared with 4.8 months (p=0.017, log-rank test). The median progression-free survival time was 7.5 months in the combination group compared with 1.7 months in the control group (p=0.004, log-rank test). The study revealed that both overall survival and progression-free survival in the combination group were significantly longer than that in the control group. From this work it can be concluded that cyproheptadine may significantly improve survival outcomes of sorafenib-treated advanced hepatocellular carcinoma patients.

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