

Cytotoxic activity of the novel dual PI3K/mTOR inhibitor NVP-BGT226 in both normoxic and hypoxic hepatocarcinoma cells

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Hepatocellular carcinoma (HCC) is one of the most common lethal human malignancies worldwide. One of the most prevalent causes for the high mortality rate in patients with HCC is the lack of effective treatment, especially for patients with advanced disease (1). For this reason, an effective and well-tolerated pharmaceutical profile for the treatment of advanced HCC is requested to introduce new, potential therapeutic approaches. We evaluated the cytotoxic effect of the orally bioavailable dual PI3K/mTOR inhibitor, NVP-BGT226, on a panel of HCC cell lines, since hyperactivated PI3K/Akt/mTOR signaling pathway could represent a biomolecular target for Small Inhibitor Molecules in this neoplasia (2). We analyzed the activity of the drug in both normoxia and hypoxia conditions, which play often a relevant role in the induction of chemoresistance and angiogenesis. Indeed, it has been recently demonstrated that PI3K/Akt signaling pathway regulates VEGF and HIF-1 α expression, and inhibitors targeting PI3K p110 α decrease both VEGF expression and angiogenesis in an vitro HCC model. In normoxia NVP-BGT226 caused cell cycle arrest in the G₀/G₁ phase of the cell cycle and induced apoptosis and autophagy at low concentrations. Interestingly, the drug inactivated p-Akt and p-S6 at a concentration lower than 10 nM. In hypoxia NVP-BGT226 maintained its cytotoxic efficacy at the same concentration, as documented by MTT assays and Western blot analysis. Moreover, in hypoxia the drug showed inhibitory properties against angiogenesis by lowering the expression of the transcription factor HIF-1 α and of VEGF. Our results indicate that NVP-BGT226 has a potent cytotoxic effect on HCC cell lines also in hypoxia condition, thus emerging as a potential candidate for cancer treatment in HCC targeted therapy.

References

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- [2] Simioni C et al (2013) The AKT inhibitor MK-2206 is cytotoxic in hepatocarcinoma cells displaying hyperphosphorylated AKT-1 and synergizes with conventional chemotherapy. *Oncotarget*, 4:1496-1506.

Keywords

Hepatocellular carcinoma; NVP-BGT226; Hypoxia; targeted therapies.