PI3Kα-selective inhibitor alpelisib (BYL719), may be effective as anticancer agents in Rhabdomyosarcoma

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Rhabdomyosarcoma (RMS) is a highly malignant and metastatic pediatric cancer that arises from the skeletal muscle. Recent studies have identified an important role of AKT signaling in RMS progression. This suggests targeting components of the PI3K/Akt pathway may be an effective therapeutic strategy. Here, we investigated the in vitro activity of the class I PI3K inhibitors [1] in human rhabdomyosarcoma cell lines (embryonal rhabdomyosarcoma RD and A204, alveolar rhabdomyosarcoma SJCRH30). We used a panel of four compounds which specifically target PI3K isoforms including the PI3K α -selective (p110 α) inhibitor alpelisib BYL719, currently in clinical development by Novartis Oncology, the p110β TGX-221 inhibitor, the p110 γ CZC24832, the p110 δ CAL-101inhibitor and the dual p110 α /p110 δ inhibitor AZD8835. The effects of single drugs and of several drug combinations were analyzed to assess cytotoxicity by MTT assays, cell cycle by flow cytometry, apoptosis by caspase 3/7 assay and Western blot, as well as the phosphorylation status of the pathway. BYL719 treatment resulted in G1 phase cell cycle arrest and apoptosis. BYL719 administered in combination with CAL-101, for 48 h and 72h, decreased cell viability and induced apoptosis in a marked synergistic manner. Taken together, our findings indicate that BYL719, either alone or in combination with p1108 CAL-101inhibitor, may be an efficient treatment for human rhabdomyosarcoma cells that have aberrant upregulation of the PI3K signaling pathway for their proliferation and survival.

References

[1] PI3K inhibitors as new cancer therapeutics: implications for clinical trial design. Massacesi C Di Tomaso E Urban P Germa C Quadt C et. al. OncoTargets and Therapy 2016 vol: 9 pp: 203

Keywords

Rhabdomyosarcoma, PI3K/Akt pathway, cancer