EFFECT OF PAZOPANIB MONOTHERAPY VERSUS COMBINATION WITH TOPOTECAN IN ANAPLASTIC THYROID CANCER

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Introduction: Anaplastic thyroid cancer (ATC) is among the most aggressive malignancies with poor prognosis. ATC is not sensitive to any current systemic therapies and news treatments options are needed. The aim of the present study was to determine the activity of the combination pazopanib/topotecan vs. pazopanib or topotecan monotherapy on ATC cells.

Methods: Proliferation assays were performed on ATC cell lines (8305C and FB3) exposed for 72h to pazopanib and topotecan alone and their combination. The combination of pazopanib with topotecan was explored on 8305C and FB3cells in a fixed molar concentration ratio (1:10), respectively. Synergism was quantified by the combination index (CI) method. The concentration of topotecan lactone on treated cells was measured using high-performance liquid chromatography (HPLC) method. Modulation of ATP-binding cassette transporter G2(ABCG2), vascular endothelial growth factor (VEGF), hypoxia-inducible factor 1α (HIF-1α) and colony stimulating factor 1(CSF-1) gene expression was evaluated by real time PCR analysis.

Results: The 72h pazopanib exposure inhibited the 8305C and FB3cell proliferation with an IC_{50} of 25080$\pm$3220 nM and 18020$\pm$1307nM, respectively. A higher antiproliferative effect was found using topotecan on 8305C and FB3cell lines, as demonstrated by the calculated IC_{50s} of 307.3$\pm$4.82nM and 0.65$\pm$33nM, respectively. Simultaneous exposure of 8305C and FB3cells to different concentrations of pazopanib and topotecan for 72h showed a strong synergism for all the fraction of affected cells with a CI<1. Moreover, the simultaneous combination of pazopanib and topotecan increased the intracellular concentrations of topotecan lactone. Furthermore a decrease of the gene expression of ABCG2, VEGF, HIF-1α and CSF-1was shown in combination-treated ATC cells.

Conclusions: The simultaneous combination of pazopanib and topotecan demonstrated a highly synergistic ATC antitumor activity, suggesting a possible and rapid translation of this schedule into clinical trials. The study has been supported by a grant from Associazione Italiana per la Ricerca sul Cancro (IG-17672) to GB.

Keywords: pazopanib, topotecan, anaplastic thyroid cancer, synergism, gene expression