The synergistic activity of irinotecan and sunitinib in anaplastic thyroid cancer: a new combined treatment approach

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Background. Anaplastic thyroid cancer (ATC) is among the most aggressive malignancies with extremely short survival and poor prognosis (Smallridge RC et al., 2009). No curative options are available for patients with ATC, and identifying new therapeutic strategies is critical for ATC management. Classical cytotoxic drugs have demonstrated limited or no activity in ATC when administered alone (Alonso-Gordoa T et al., 2015), whereas, the improvement in the recognition and comprehension of genetic and molecular alterations underlying the development of ATC (e.g. mutational activation of BRAF), led to the development of new treatment options (Begum S et al., 2004) such as tyrosine kinase inhibitors (TKIs). Despite several preclinical studies on TKIs have shown an *in vivo* antitumor activity in ATC (Kim S et al., 2007; Di Desidero T et al., 2013), monotherapy may be not so clinically effective. In this perspective, the aim of this study is to determine the activity of irinotecan, a classic chemotherapeutic drugs, in combination with sunitinib on ATC cells. **METHODS.** Proliferation assays were performed on ATC (8305C, FB3) cell lines exposed to SN38, the active metabolite of irinotecan, and sunitinib (SU) with three different treatment schedules in ATC cells: simultaneous exposure, sequential exposure and reverse exposure. The total exposure of each drug was 72 h. The synergism was determined with the method by Chou and quantified by the combination index (CI). ABCG2, ANG2, C-met, CXCR4, CSF-1, CSF-3, Hif1α and VEGF gene expression were performed with realtime PCR. 8305C xenografts in nude mice were treated with irinotecan (CPT-11 100 mg/Kg/wk) and sunitinib (25 mg/kg/every two days) alone and in combination in three different schedules treatments - simultaneous and sequential, as described above and tumour volumes were measured. **RESULTS.** The simultaneous combination of SU and irinotecan (SN-38) determined a high synergism on ATC cells (CI<1 and DRI>1). Moreover, the synergism of the combination schedule, in particular for the simultaneous one, greatly modulated the expression of several angiogenesis-related genes, such as Ang-2, Cmet, VEGF, Csf-1, Csf-3, CXCR4 and Hif-1α in ATC cells. A significant *in vivo* antitumour effect on 8305C xenografts was observed with the simultaneous combination of irinotecan and sunitinib, resulting in a significant tumour regression after 26 days of treatment (e.g. at day 21, 420.72 mm^3 *vs.* 1974.7 mm^3 of SU treated group, P<0.05). **CONCLUSIONS.** The simultaneous combination of irinotecan and SU, *in vitro* and *in vivo* demonstrated a highly significant, synergistic antitumor activity in ATC cells suggesting a possible translation of this schedule into the clinics.

Smallridge RC, Marlow LA, Copland JA (2009). Endocr Relat Cancer 16, 17-44.
Alonso-Gordoa T, Diez JJ, Duran M, Grande E (2015). Ther Adv Med Oncol 7, 22-38.
Begum S, Rosenbaum E, Henrique R, Cohen Y, Sidransky D, Westra WH (2004). Mod Pathol 17, 1359-1363.
Kim S, Yazici YD, Calzada G, Wang ZY, Younes MN, Jasser SA, El-Naggar AK, Myers JN (2007). Mol Cancer Ther 6, 1785-1792.
Di Desidero T, Fioravanti A, Orlandi P, Canu B, Giannini R, Borrelli N, Man S, Xu P, Fontanini G, Basolo F, et al. (2013). J Clin Endocrinol Metab 98, E1465-1473.