Colon cancer therapy beyond tumor progression: evaluation of the effects of switched schedules and related pharmacodynamic biomarkers.

1)Di Desidero T. 2)Orlandi P. 3)Fioravanti A. 4)Cremolini C. 5)Antoniotti C. 6)Loupakis F. 7)Falcone A. 8)Bocci G.

University of Pisa

Background. The combination of bevacizumab with fluoropyrimidines and irinotecan-based chemotherapy is a standard first-line treatment option in metastatic colorectal cancer (mCRC). Clinical data suggest that the continuation of bevacizumab beyond tumor progression during second-line chemotherapy could also be beneficial [1,2].

METHODS. In vivo studies were performed in nude mice subcutaneously transplanted with HT-29 Braf mutated colon cancer cells, in order to evaluate the differences, in term of pharmacodynamic biomarkers, between non-resistant and resistant tumors. The performed treatments included drug combinations with a switch between chemotherapeutic (i.e., irinotecan and 5-fluoruracil) and/or antiangiogenic drugs (i.e., bevacizumab and sunitinib). Tumour volumes were measured. Plasma samples were collected for ELISA testing and tissue immunohistochemistry was performed. In vitro studies. Proliferation assays were achieved on colon cancer (HT-29, Caco-2) cell lines exposed to SN-38, the active metabolite of irinotecan, and sunitinib alone or in combination for 72 h. The synergism was determined with the method by Chou and quantified by the combination index (CI) [3]. ABCG2 gene expression were performed with real-time PCR and SN-38 intracellular concentrations were measured by high-performance liquid chromatography.

RESULTS. The progression of tumors treated with antiangiogenic drugs and irinotecan alone arose earlier than the ones with the combination treatments, which strongly delayed the onset of clear unresponsiveness of the tumor masses until day 75. The data showed that the switch in the combined treatments, at the time of tumor relapse, of the chemotherapeutic (from irinotecan to 5-fluoruracil), or the antiangiogenic drug (from bevacizumab to sunitinib) or of both drugs induced a new response, suggesting a potent chemosensitization effect. Immunohistochemistry analyses of PDGF-C, PlGF, SD1-α, Tie-2, and VEGFR-2 showed statistical differences between tumors at the time of relapse and after the switched therapy. To study the chemosensitization effect of sunitinib, the combination treatment of SN-38, and sunitinib was tested in vitro. The simultaneous combination of SN-38 and sunitinib determined a strong synergism on HT-29 colon cancer cells (CI<1 and DRI>1), with a significant inhibition of the ABCG2 gene expression. Based on these findings, the intracellular concentration of the active drug was measured, showing higher SN-38 concentrations in cells exposed to the combined schedule.

CONCLUSIONS. The switch of one or both drugs at the time of tumor progression of the combined treatment determined a significant tumor response, with a significant modulation of angiogenic markers and a possible variation of intracellular drug concentration.

REFERENCES

[1] Grothey A, et al. Response-independent survival benefit in metastatic colorectal cancer: a comparative analysis of N9741 and AVF2107. J Clin Oncol 2008, 26: 183-9.

[2] Masi G, et al. Continuation or reintroduction of bevacizumab beyond progression to first-line therapy in metastatic colorectal cancer: final results of the randomized BEBYP trial. Ann Oncol. 2015 Apr;26(4):724-30.

[3] Chou TC (2006). Theoretical basis, experimental design, and computerized simulation of synergism and antagonism in drug combination studies. Pharmacol Rev 58, 621–681.