ET-09. DECOY OLIGONUCLEOTIDE DERIVED FROM MGMT ENHANCER HAS AN ANTINEOPLASTIC ACTIVITY IN-VITRO AND IN-VIVO
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INTRODUCTION: Silencing of O(6)-methylguanine-DNA-methyltransferase (MGMT) in tumors, correlates with a better therapeutic response and with increased survival. Our previous results demonstrated the pivotal role of NF-kappaB in MGMT expression, mediated mainly through binding of p65/NF-kappaB homodimers to the non-canonical NF-KappaB motif (MGMT-kappaB1) within MGMT enhancer. METHODS AND RESULTS: In an attempt to attenuate the transcription activity of MGMT in tumors we designed locked nucleic acids (LNA) modified decoy oligonucleotides corresponding to the specific sequence of MGMT-kappaB1 (MGMT-kB1-LODN). Following confirmation of the ability of MGMT-kB1-LODN to interfere with the binding of p65/NF-kappaB to MGMT enhancer, the potential of the MGMT-kB1-LODN to enhance cell killing was studied in vitro in two glioma cell lines (T98G and U87) and a melanoma cell line (A375P). All three cell lines manifested a significant enhanced cell killing effect following exposure to temozolomide (TMZ) when first transfected with MGMT-kB1-LODN, and also induced a significant cell killing when administered as monotherapy. These results were confirmed also in-vivo on A375P Melanoma xenografts. Intratumoral (Intralresional - IL) injection of MGMT-kB1-LODN with or without IP injection of TMZ induced significant tumor growth inhibition either as a monotherapy or in combination with TMZ. The long-term effect of MGMT-kB1-LODN monotherapy was evaluated using a repetitive IL injection every 4 to 5 days for 35 days with either MGMT-xB1 LODN or control ODN or vehicle. A significant difference (p < 0.01) in tumor volume was obtained by MGMT-kB1-LODN compared to both control groups. Moreover, two out of the seven mice treated with MGMT-xB1-LODN demonstrated tumor regression by day 35 and no tumor recurrence was observed five months later. CONCLUSION: The results of these experiments show that the MGMT-kB1-LODN has a substantial antineoplastic effect when used either in combination with temozolomide or as monotherapy. Our results suggest that MGMT-kB1-LODN may provide a novel strategy for cancer therapy.