Background: We have recently reported that aberrant DNA hypomethylation down regulates the expression of components of the "tumor recognition complex" (i.e., HLA class I antigens, tumor-associated antigens belonging to the cancer/testis antigens (CTA) class and accessory/co-stimulatory molecules) in neoplastic cells of different histotypes. These evidences strongly suggest that the extent of DNA methylplification of the house-keeping gene MAGE-A3 promoter in solid tumors is strictly related to the response of neoplastic cells to immunotherapy. In this context, the present study was designed to evaluate the immunomodulatory potential of new DNA demethylating agents (DHA) on neoplastic cells from solid tumors, aiming to identify novel strategies to improve the clinical response to cancer immunotherapy.

Materials and methods: Cytosolic RNA, microsomal, renal cell carcinoma and sarcoma cell lines were treated in vitro with the new DNA SGI-110, a dioxolane of 5-aza-2'-deoxycytidine, that are for both DNA demethylating and DNA hypermethylation. These evidences strongly suggest that SGI-110 may represent an attractive therapeutic agent to comprehensively increase immunogenicity and immune recognition of neoplastic cells from solid tumors and provide the scientific rationale for its clinical development to design new and possibly more effective chemotherapeutic approaches in patients with solid malignancies.

RESULTS

Human melanoma cells either untreated (solid orange) or treated with 1 µM SGI-110 (empty green) were sequentially incubated with the HLA-A2-restricted gp100-specific CTL, MEL 275 melanoma cells untreated (solid purple), or treated with 1 µM SGI-110 (empty green), were sequentially incubated with the HLA-A2-restricted gp100-specific CTL.

CONCLUSIONS

This study has identified novel immuno-biological activities of SGI-110.

Specifically:

- SGI-110 persistently increased the expression of CTA in solid malignancies of different histotypes through the DNA hypomethylation of their promoter region
- SGI-110 strongly up-regulated the constitutive levels of CTA expression in solid malignancies of different histotypes
- SGI-110 up-regulated the expression of HLA class I antigens, HLA-A2 allostery and of the co-stimulatory molecule ICAM-1 on neoplastic cells
- Phenotypic changes induced by SGI-110 on neoplastic cells significantly (p<0.05) increased their lysis by tumor antigen-specific CTL

Altogether, these evidences demonstrate that SGI-110 represents an attractive therapeutic agent to comprehensively increase immunogenicity and immune recognition of neoplastic cells from solid malignancies of different histotypes, and provide the scientific rationale for its clinical development to design new and possibly more effective chemotherapeutic approaches in patients with solid malignancies.