NOVEL STRATEGIES FOR COMBINING IMMUNOTHERAPY WITH CHEMOTHERAPY: FROM THE PRECLINICAL STUDIES TO THE CLINICAL EXPERIMENTATION

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More than a century of observation and research have shown that the natural responses of the organism, especially the immune responses , have a fundamental role in controlling the development of tumors.

Because of its low toxicity and its specificity, immunotherapy may represent a biological tool in cancer therapy, complementary to current standard treatments (surgery, chemotherapy, radiotherapy) . However , an obstacle is interposed between a good anti-tumor response and the eradication of the tumor itself. Such an obstacle is represented by "cancer immunoediting ", a process through which the tumor , in its progressive development, mutes and blinds the immune responses making the organism tolerant to cancer development. Only the resetting of the immune system may allow to overcome this problem .

Cyclophosphamide is a chemotherapeutic alkylating agent of the first generation widely used in various antineoplastic drug cocktails and considered immunosuppressive. Studies carried out in recent years have shown that cyclophosphamide has a amount of new features. In fact, it reduces the number of regulatory T cells (with immunosuppressive activity) but , above all, subsequently to its discontinuation, it induces a considerable production of immunostimulating factors (various types of interleukins and chemokines) which are responsible of a significant increase of the adaptive immunity leading to the the proliferation and activation of lymphocytes and to their migration in the tumor , as well as of the innate immunity with a subsequent raise in the frequency of dendritic cells.

A therapeutic strategy based on a single injection of cyclophosphamide immediately followed by the administration of a tumor vaccine has been shown to induce significant tumor regressions in experimental models . This strategy, applied to patients undergoing surgery for melanoma metastases in a phase I study, gave similar results. Further studies are needed to define the optimal treatment modalities and the type of tumors susceptible, but the path traced allows us to consider this strategy as an effective tool to prevent relapses in cancer patients already freed from the primary tumor