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Multi-peptide immunotherapy in combination with immunogenic chemotherapy in refractory cancer patients

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Background:
Despite the recent understanding that refractory cancer is immunogenic and the level of tumor infiltrating T-cells identified is associated with disease outcome; few studies evaluate the multi peptide immunotherapy of the refractory disease. Antigen-specific active immunotherapy targeting refractory cancer is limited and focus on only a few antigens clinically irrelevant antigens. Overexpression of self-proteins that are involved in cancer proliferation has been shown to be a mechanism by which self-proteins become immunogenic. We questioned whether overexpressed proteins that are found in high incidence in several refractory malignancies and associated with poor prognosis could be refractory tumor clinically relevant targets to develop multi peptide immunotherapies in combination with other approaches such as immunogenic chemotherapy. We questioned whether multi peptide immunotherapy targeting twenty antigens could be an approach to the development of refractory cancer immunotherapy in patients with good ECOG despite their prognosis. Methods: Forty proteins overexpressed in refractory cancer and associated with these clinical conditions were identified. Indirect ELISA was used to evaluate antibody immunity directed against these proteins in 25 refractory cancer patients and 100 age-matched controls. Web-based algorithms were used to identify long peptides including both Class I and Class II binding epitopes derived from the native protein sequences. Peptide reactivity was assessed using Granzyme B ELISPOT. Peptides that were highly immunogenic by ELISA and ELISPOT were formulated into multi-peptide immunotherapy and patients were enrolled in a pilot clinical trial approved by the local ethic committee. 25 patients were treated with intradermal peptide injections in 8 times in the area of the axillary and inguinal lymph nodes and afterwards we administered the peptides in the areas with tumor activity according with the CT scans along with Doxorubicin and Oxaliplatin as immunogenic chemotherapy after dose-response of both drugs was tested in vitro using autologous PBMC???s and the patients were monitored for the development of Th1 and CD8 immune response and clinical response. At specific time points, subjects were evaluated clinically by CT scans. Tumor sections from the original surgery were stained for CD8 and Th1 positive cells by immunohistochemistry. CD8 T-cell and Th1 quantitation was based on the mean of three 40X fields per section. Results: Bcl-2, RCAS1, VCP, FAP, Survivin, fascin, EGFR and Ape-1 are immunogenic in refractory cancer patients. Serum IgG + IgM + IgA responses for all the peptides derived from the mentioned proteins were significantly elevated in refractory cancer patients sera when compared to donor controls (Bcl-2 p=0.0001, RCAS1 p=0.0001, VCP p= 0.005, FAP = 0.0001, survivin 0.003, fascin p= 0.001, EGFR p=0.005 and Ape-1 p=0.0001). ELISPOT screening yielded epitopes that were immunogenic in refractory cancer. Tumors were significantly inhibited after the treatment with the combination of the multipeptide antigen specific active immunotherapy and immunogenic chemotherapy with significantly increased in tumor infiltrating CD8 T-cells and Th1 cells and decreased Foxp3 positive cells.

The ultimate aim of immunotherapy is to boost the body's immune system to destroy tumor cells and to provide a durable antitumor immune response. The strategy of using monoclonal antibodies against two distinct inhibitory receptors on T-cells, PD1, and CTLA-4 is a major breakthrough in the field of cancer immunotherapy. The efficacy of this strategy was first established in patients with metastatic melanoma based on the antitumor immune response and increased overall survival rates of patients treated with ipilimumab, a monoclonal antibody targeting human CTLA-4 [1]. The remarkable antitumor activity of PD-1/PDL-1 inhibition in melanoma, renal cell carcinoma, and NSCLC lead to regulatory approval of increasing list of anti-PD1/PDL1 antibodies in hematological malignancies and various other solid cancers [2, 3]. Nevertheless, the efficacy of PD-1/PD-L1 pathway inhibition as a monotherapy has pro Very soon it will be realized that the clinical benefit obtained from the immune checkpoint blockade is limited to only a small subset of patients and that most patients do not respond to this therapy. The combination of immune checkpoint blockade with several other anticancer treatments has shown remarkable success in various cancers and provided hope for the patients who do not respond to checkpoint inhibitor monotherapy. We have summarized the therapeutic potential of checkpoint inhibitors with drugs that increase tumor immunogenicity, reduce tumor burden, and reverse tumor-mediated immunosuppression, leading to an effective and durable antitumor immune response. In the end, we provided a novel approach to rationally design dual or triple inhibitory chemotypes that can concomitantly hit several tumor-promoting pathways and increase the immune effector response by blocking myeloid cell-mediated tumor immunosuppression. This novel approach is early in its development stage, but the promising antitumor results generated so far by use of dual or triple inhibitor chemotypes in different cancer models provide a rationale to continue exploring these agents with immune checkpoint inhibitors.vided benefit to only some of the patients while a significant fraction does not respond to this therapy.

Refference

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