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Investigation of cell therapies: a role for TIL and/or DC vaccines?

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Abstract

One category of immunotherapy, cell therapy, describes the process of infusing living cells, either via adoptive cell therapy (ACT) of cytotoxic cells or as a vaccine-based on specialized antigen presenting cells, i.e. dendritic cells (DC). ACT in the form of tumor-infiltrating lymphocytes (TIL) has shown encouraging results in patients with metastatic melanoma. However, clinical effect of TIL therapy has so far not been proven in other solid tumors, including gynaecological cancers. To further improve clinical responses in patients with melanoma we implemented a unique treatment strategy of TIL therapy combined with a DC-based cancer vaccine, clinical trial MAT02 (NCT01946373). The results are encouraging showing one patient with a strong partial response (PR, 8 years without disease progression), two patients with a complete response (CR, 7and 6 years), and one patient with a mixed response (4/4 fully treated patient responding). Cervical cancer has been shown to have an influence of reactive oxygen species (ROS) in tumor progression and that patients in later stages of cancer have ROS levels creating a hostile tumor microenvironment. We have established a strategy to render human cytotoxic lymphocytes resistant towards ROS by Nrf2-activation of intrinsic anti-oxidant responses. We hypothesize that a Nrf2 activation in TIL before infusion could enhance the efficacy of adoptive cell therapy within these patients. Our Aim is to initiate the first TIL trial for cervical cancer patients in Sweden, during 2025.
Unfortunately, clinical trials using DC vaccine as a monotherapy has shown it to be safe but with an overall response rate rarely exceeding 15%, leaving room for improvement. We are currently evaluating different pre-treatment conditions for generation of whole tumor lysate aiming to improve the activation capacity of a therapeutic whole tumor lysate DC vaccine. For this, several protocols for generation of whole tumor lysates are compared, including the “golden-standard”, pre-treatment protocols used in clinical trials, as well as novel pre-treatment protocols. Our preliminary data shows that modification of the pre-treatment of the tumor cells before generation of tumor lysate is enhancing the capacity of the DC vaccine to activate CD8+ T cells. We are currently focusing on the mechanism behind the increased the immunogenicity observed for some tumor lysates.
We aim to be able to use an improved DC vaccine in combination with checkpoint inhibitors (ICI) in the near feature to treat patients with endometrial or cervical cancer, who now receives ICI within the standard of care program in Sweden.