Estimation of antitumor activity of chemoimmunotherapy with nanoconjugates of methotrexate and vaccines based on dendritic cells with silenced IL-10 receptor expression

The use of dendritic cell (DCs)-based vaccines in anti-cancer therapy is a promising strategy for preclinical and clinical trials. However, despite of DC's great potential to stimulate a specific anti-tumor immune response, the therapeutic effect observed after their administration is moderate. Factors influencing this include, but are not limited to, the presence of interleukin-10 (IL-10) in the tumor microenvironment (TME), which hampers the proper function of DCs. Therefore, attempts are being made to prepare DCs capable of initiating an efficient anti-tumor immune response in adverse environmental conditions. Moreover, in order to improve the effectiveness of immunotherapy, the treatment strategies are supplemented with the administration of cytostatics which administered in an appropriate dose, lead to the cancer cells elimination and the modulation of the immune response. Furthermore, this effect can be enhanced by the use of cytostatics attached to carriers ensuring more efficient accumulation of drug in the tumor tissue.

The aim of this study was to determine the antitumor activity of chemoimmunotherapy with methotrexate and hydroxyethyl starch nanoconjugate (HES-MTX) applied in immunomodulating dose and supported by vaccines based on mature DCs with IL-10 receptor silenced expression (DC/IL-10R/TAg) in murine colon carcinoma MC38 model.

The use of nanoconjugate in the dose of 20 mg/kg contributed to the modulation of the immune response and inhibition of tumor growth. This treatment resulted in an increase in the size of the effector cell populations and an enhancement of their cytotoxic activity. Consequently, beneficial conditions for initiation of an anti-tumor immune response by injected peritumorally mature DC were created. However, due to the presence of IL-10 in TME, the immune response was impaired. In order to solve this obstacle, the expression of the IL-10 receptor in DCs was downregulated. This, in turn, led to obtaining DCs with reduced sensitivity to the suppressive influence of this cytokine. The application of the therapy consisting of an immunomodulating dose of HES-MTX and DC/IL-10R/TAg caused a significant inhibition of MC38 tumor development. This was due to the increased influx of effector cells into the tumor tissue, accompanied by a reduction in the size of the population of cells with suppressor activity, as well as the induction of an efficient and specific anti-cancer immune response.

The results presented in this study indicate that a favorable environmental niche was created after the administration of 20 mg/kg of HES-MTX. This enabled the DC to develop an anti-tumor immune response, and the therapeutic effect was enhanced as a result of the use of DCs with decreased sensitivity to the influence of IL-10 present in MC38 tumor.