CD74 Targeted Nanoparticles as Dexamethasone Delivery System for B lymphoid Malignancies

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ABSTRACT

Chronic Lymphocytic Leukemia (CLL) is the most common adult leukemia and is not curable with standard therapy. In CLL the B lymphocytes appear morphologically mature but immunologically express less mature B cell makers. Specifically, the CLL B cells co-express surface antigens including CD19, CD20, CD5, CD23. Due to nonspecific delivery of chemotherapeutics to malignant as well as normal cells, patients experience numerous side effects. Targeted drug delivery to cancer cells is a desirable goal for all anti cancer strategies.

Corticosteroids are beneficial and well established part of CLL treatment. Dexamethasone(DEX) is frequently used in CLL therapies as well as other malignancies and antiinflammatory diseases. However, DEX non specifically enters all tissues inducing various toxicities to patients. Therefore, DEX treatment is often discontinued or not administered to certain patients.

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We aimed to deliver this efficient clinical agent via a targeted delivery vehicle and examine its effect on its target B-CLL cells. The main scope of the work presented is the creation of a sterically stable nanoparticle, an immunoliposome that has DEX encapsulated in its interior and anti-CD74 monoclonal antibody (Mab) in its exterior, targeting CLL B cells expressing the surface antigen that is recognized by the Mab. CD74 liposome without drug was shown to be cytotoxic in vitro in cell lines and B CLL cells and to mimic cytotoxicity of anti-CD74 in vivo. CD74 liposome showed high binding to malignant cells expressing the antigen and induction of leukemic cell apoptosis. Furthermore, a methodoly was developed to quantitate DEX in vitro and in vivo using Liquid Chromatography tandem Mass Spectometry (LC/MS-MS). The method was adjusted to measure encapsulated DEX in plasma and was applied in a pilot pharmacokinetic study in mice. The liposomal DEX targeted with anti-CD74 was evaluated in vitro in cell lines and primary CLL B cells and showed potent cytotoxicity. Immunoliposome efficacy was subsequently, tested in vivo in a mouse model of lymphoid disease and showed to significantly increase survival of diseased mice compared to controls. Overall, the studies showed therapeutic effect of CD74 DEX Liposome and advantage of encapsulating the drug into immunoliposome. Additionally, we obtained in vivo evidence demonstrating that nontargeted DEX Liposome was protective against non desirable effects of free dexamethasone. The work presented provides evidence that DEX immunoliposomes can have therapeutic effect in B cell malignancies with the possibility to be applied in other disease in which corticosteroids are administered.