MASTER'S THESIS DEFENSE

Inhibition of Lymphatic Metastasis Using Calcium Phosphate Nanoparticles Loaded with Cisplatin

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Abstract:

A new targeted therapy has been developed to deliver chemotherapy directly to the lymph nodes for treatment of lymphatic metastasis. Localization of chemotherapy was accomplished by using nanoparticles of calcium phosphate (nanoCaP) as the delivery vehicle. The chemotherapy drug cisplatin (CDDP) was adsorbed to the exterior of the nanoCaP to form the nanoconjugates (nanoCaP/CDDP). A new murine model for lymph node metastasis was developed in order to assess *in vivo* efficacy. In the model, primary tumors were created in the rear footpad of female BALB/C mice by injection of 66cl4 mouse breast cancer cells. Cells from the primary tumors were found to metastasize to the draining popliteal node after approximately one week as evidenced by tumor cell colony formation in cultured lymph nodes. Five different animal studies were conducted to evaluate the effectiveness of the nanoCaP/CDDP against lymph node metastasis. The treatment groups for each study were: intratumoral nanoCaP/CDDP, intratumoral sham PBS injection, or intraperitoneal CDDP. Intraperitoneal administration of CDDP results in systemic, whole-body drug exposure which is the standard of care and thus the positive control group. Treatment was given one time only at 7 – 18 days after cell injection, except for study 4. Study 4 mice received three injections spaced three days apart. Lymph node metastasis was quantified on between days 19 – 25. The number of cancer cells in the popliteal lymph node was determined by counting colonies that grew during culture of retrieved lymph nodes. Daily mouse weights and primary tumor size at time of sacrifice were recorded. Number of colonies in study 1 was as follows: nanoCaP/CDDP 33±43, systemic therapy 13±20, and controls 142±170. No significant difference was found between nanoCaP/CDDP and systemic therapy ($P>0.05$, T-test), but there were significant differences (Rank Sums, Kruskal-Wallis, $P<0.05$) between (1) nanoCaP/CDDP vs. control and (2) systemic therapy vs. control. Mice treated with nanoCaP/CDDP group slightly increased their original body weight by 2±3%, while the systemically treated mice lost 12±5% of their original weight and 5 of the 7 systemically treated mice died due to CDDP side effects. When compared, there was statistical significance between the treatments ($P<0.05$, T-test). The results from these studies show that (1) the new mouse model can be used to reproducibly generate lymphatic metastases in the draining popliteal node, and (2) nanoCaP/CDDP are as effective as conventional systemic therapy of CDDP and have the advantage of reducing debilitating, and potentially lethal, side effects of chemotherapy.