MODULAR POLYMER PLATFORM THAT DELIVERS CYTOKINES AND CISPLATIN IS EFFECTIVE IN REDUCING TUMOR BURDEN IN AN ANIMAL MODEL OF HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC)

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OBJECTIVE

Head & Neck Squamous Cell carcinoma (HNSCC) is the sixth most common cancer in the world. Aggressive surgical resection and chemoradiation (CRT) is the cornerstone of treatment of disease; this though, can be disfiguring and may also affect everyday functioning, with a profound impact on quality of life. Investigations are needed for methods of reducing tumor burden and side effects in advanced and unresectable disease.

RESULTS

- Cisplatin Secreting Polymer Reduces Tumor Burden in HN CA (Figure 1): Our results using this novel polymer platform demonstrate a significant reduction in tumor growth. The cisplatin secreting polymer effectively reduced SCCVII/SF tumors in the C3H/HeJ mice by over 16-fold (P < 0.01) as compared to control, plain polymer, and plain polymer + intratumoral cisplatin injection groups.
- Cisplatin Secreting Polymer Enhances the Efficacy of Radiation Therapy (Figure 2): We also observed a statistically significant lower tumor weight among mice treated with cisplatin polymer and concomitant radiation compared to the radiation alone group and the control group.
- DC-CCL21 Secreting Polymer Reduces Tumor Burden in HN CA (Figure 3): The DC (dendritic cell)-CCL21 (cytokine marker) polymer reduced SCCVII/SF tumors in the C3H/HeJ mice by over 41% compared to the control groups (p<0.01).

CONCLUSIONS

1. We demonstrate the efficacy of a novel polymer platform in delivering cisplatin and cytokines to a partially resected SCC in a murine model.
2. We also demonstrate that we can effectively grow dendritic cells in the polymer that can actively secrete CCL21 for a minimum of five days.
3. Our results indicate that this polymer may represent a new therapeutic modality for patients with HNSCC. Once this polymer platform is optimized we will plan for validation in the context of a prospective trial in patients with unresectable advanced or recurrent HNSCC.

MATERIALS AND METHODS

- Study Design: in vivo study.
- Polymer Fabrication: The cisplatin-releasing polymer was designed to be adequately flexible to adapt to irregular tissue contours without tearing. To meet this requirement, a wide range of mixing ratios involving two polymers: poly-ε-caprolactone (PCL) and a co-polymeric blend of poly(DL-lactide-co-ε-caprolactone) (PLCL), were evaluated in a pilot study. A 70:30 ratio of PLCL-PCL was found to offer the optimal flexibility and malleability of the PCL sheet, allowing for more facile handling by surgeons during implantation in vivo.
- Mouse model: 4 x 10^4 cells from the well established C3H/HeJ mouse SCCA cell line SCCVII/SF were injected into 6-week-old C3H/HeJ mice. Eight mice were injected in each group unless otherwise specified. All mice were injected subcutaneously over the right flank. Tumor size was measured until the mice were euthanized. PolyIon Study: C3H/HeJ mice were randomized to receive implantation of (1) no polymer, (2) plain polymer; (3) plain polymer with local cisplatin injection; (4) cisplatin polymer. The two groups of mice implanted with cisplatin polymer or no polymer were further randomized to receive (1) 4 Grays external beam radiation for 4 days; (2) no radiation.
- Radiation Therapy: After tumor debulking animals were assigned to various treatment groups. For the RT experiments, the treatment groups were: (1) No treatment (no polymer and concomitant radiation); (2) No treatment (no polymer alone); (3) No treatment (no polymer + RT); (4) cisplatin polymer alone; (5) cisplatin polymer + RT. On post-surgical day number three, the mice were anaesthetized and positioned in a Lucite jig with lead shielding the body, except for the tumor site, which was irradiated using a Gamma cell 40 irradiator at a dose rate of approximately 0.6 Gy/min. Tumors were irradiated with a total dose of 16Gy given in 4Gy fractions on 4 consecutive days.
- Cytokine Study: mice were grouped into: (1) no polymer; (2) plain polymer; (3) plain polymer with intratumoral injection of recombinant CCL21 twice a week; (4) polymer containing parental dendritic cells; (5) polymer containing dendritic cells secreting CCL21 (DC-CCL21).

REFERENCES