Abstract

Objective: To evaluate the therapeutic efficacy of a novel modular polymer platform in the treatment of HNSCC.

Study Design: In vivo study.

Setting: Academic research laboratory.

Subjects and Methods: C3H/HeJ mice and SCID Beige 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 or no polymer were further randomized to receive (1) 4 Grays external beam radiation for 4 days; (2) no radiation. Tumor size was measured until the mice were euthanized. At necropsy, the tumors were excised and weighed. Results: Our results using this novel polymer platform demonstrate a significant reduction in tumor growth. The cisplatin-secreting polymer effectively reduced tumor growth in SCID mice by 17 fold (P < 0.01); and 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. We also observed a statistically significant longer tumor weight among mice treated with cisplatin polymer and concomitant radiation compared to the radiation alone group and the control group.

Conclusion: Herein we demonstrate the efficacy of a novel polymer platform in delivering cisplatin to a partially resected SCC in a murine model. Our results suggest 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.

Background

Head & Neck Squamous Cell carcinoma (HNSCC) is the sixth most common cancer in the world. Patients with HNSCC are at risk of mortality with more than 300,000 deaths attributable to the disease annually. Aggressive surgical resection, with or without adjuvant radiation therapy (CRT) is the cornerstone of treatment for early disease. In many patients, the necessary surgery can be disfiguring and may also affect everyday functionality, with profound quality of life consequences. During the past 30 years, the 5- to 10-year survival rate of patients with advanced T3 and T4 HNSCC has remained poor (20-30%) despite considerable advances in surgical techniques and irradiation delivery and improvements in chemotherapeutic strategies. Because 50% of the patients with advanced and unresectable disease fail primary management, salvage these patients is of paramount importance.1 Many of these patients receive radiation and chemotherapy (RT) as definitive or adjuvant therapy, which makes retreatment a challenge. Currently, the standard of care for recurrent disease is surgical salvage. Unfortunately, many advanced head and neck cancers are unresectable due to their proximity to vital structures such as the carotid artery or the skull base. Although palliation by chemotherapy is often attempted, systemic toxicity and its impact on the quality of life of patients prevents its wider clinical application. Given these dismal figures, new advances are needed in the effective treatment of HNSCC.

Development of a Novel Polymer

The science of polymer technology for drug delivery has evolved considerably since 1960. Polymers have been developed to deliver different types of drugs, including anticancer agents and antibiotics. Because most head and neck cancers and their cervical metastatic nodes are clinically accessible, local treatment with a polymer matrix may have significant clinical applications.

We have developed a novel modular drug delivery device that reproducibly reduces tumor growth in vivo. In this study, we have used a partial tumor resection model in the mouse, replicating the difficult situation we see in our patients in which the entire tumor is not resectable. The polymer platform we have developed is a flexible sheet that is designed to be applied in an intrasurgical fashion to the tumor bed to deliver the polymer to the orthotopic tumor index, thereby minimizing systemic side effects, and enhance post-operative radiation treatment.

Treatment Arms

- No polymer treatment
- Plain polymer (no cisplatin addition; only surgical debulking)
- Cisplatin polymer (+/- XRT)
- Plain polymer (no cisplatin)+ intratumoral cisplatin injection

Methods

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 polymerizable monomers with low glass transition temperature (Tg: lactide-co-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 PBS sheet, allowing for more facile handling by surgeons during implantation in vivo. Both PCL and PLCL were obtained from Boehringer Ingelheim and are manufactured under GMP and ISO-certified facilities, qualifying these materials availability for future clinical testing. Polymers were dissolved in chloroform in a 70:30 ratio of PLCL/PCL for 24 hours until gentle mixing. Fresh cisplatin was then added to the polymer solution prior to spreading on a glass or a polyethylene surface to form the thin sheets.

Animal Model Surgical Procedure. For testing the polymer platform, two animal models were used: (1) 10 × 10 mm2 cell line from the well-established human OSCC line TU686 were injected into SCID mice (2) 4 × 106 cells from the well-established human OSCC line SCCVII/SF were injected into C3H/HeJ mice. The SCCVII/SF cell line is a spontaneously arising squamous cell carcinoma syngeneic to C3H/HeJ mice. The TUB868/SF model allowed us to test the efficacy of the polymer against a human OSCC cell line. Eight mice were injected in each group unless otherwise specified. All mice were injected subcutaneously over the right flank. Tumor growth was measured and concomitant radiation compared to the radiation alone group and the control group.

Conclusion

Although the polymer used herein is currently used in FDA-approved devices, and both the cisplatin and radiation are known to be well tolerated in humans, the exact polymer-drug interactions in the vicinity of a dynamic tumor environment is unknown. In this current study, we did not explicitly evaluate biocompatibility in such an environment, and instead focused on demonstrating the overall utility of this modular approach. Now that feasibility has been demonstrated, the next step of our research program is to optimize the polymer platform to improve handling, cell delivery, and drug delivery. We propose to develop the optimal combination of the biomaterials to improve the outcome for patients with advanced or recurrent HNSCC. The modular nature of the polymer platform provides an elegant approach to future dosing modifications and device improvements, allowing for the incorporation of multiple therapeutic agents. The robustness of this design allows us to dissect underlying mechanisms of immune activation and expansion, which will in turn help us design additional strategies to block the maturation and death of the cytotoxic T cells and would therefore be anticipated in patients with aggressive HNSCC. We have obtained promising results from our pilot in vitro studies using a single layer polymer releasing cisplatin only. We are in the process of developing the optimal combination of the biomaterials to improve the outcome for patients with advanced or recurrent HNSCC. Once this polymer platform is optimized in an in vivo model, we plan for the ultimate validation in the context of a prospective trial in patients with unresectable advanced or recurrent HNSCC.

References