Scientific Abstract:

In 2001, the incidence of primary head and neck cancer in the United States was approximately 40,000[1]. The overall five year, disease specific survival rate was 64% for treated patients and the most common treatment modality remains surgery alone[2, 3]. Most patients with early stage tumors are curable with surgery or radiation therapy. Unfortunately, early stage tumors represent only approximately one third of newly diagnosed head and neck cancers. For patients who present with advanced disease at the time of diagnosis, the traditional approach of surgery and radiation therapy has been largely ineffective with cure rates of 30-50%[4, 5]. Local and/or regional failure remains the predominant pattern of failure and cause of death among the patients that recur after treatment for advanced head and neck cancer[5, 6]. The majority of patients who succumb to head and neck cancer have persistent or recurrent local and/or regional disease as the sole site of failure and 70-90% of those who develop distant metastatic disease also have local and or regional failure as a component of their failure[7, 8]. Most patients who fail regionally do so despite having undergone radiation therapy as a component of their overall treatment.

The standard of care for previously irradiated unresectable recurrent head and neck cancer has been palliative chemotherapy alone. This approach has offered limited response rates and there are no long-term survivors[9-15]. While this may be an acceptable option for patients with clearly incurable widespread metastatic disease, it may not be the best approach for those patients with only local and/or regionally recurrent disease.

For the small subset of patients with resectable local and/or regionally recurrent disease, surgical salvage is still widely regarded as the standard of care. Curative intent surgical salvage is feasible and reasonably effective in this subset of patients with 5 year survival rates from 16 - 36%[16, 17]. However, surgery in the recurrent setting is often either incomplete or impossible due to the location and extent of the tumor. Many patients will also be medically unfit for surgery or will refuse surgery based on fear of morbidity and mortality[18]. In such cases, chemotherapy and reirradiation are the only remaining treatment options.

Patients who have been previously irradiated have been shown to have three to five year survival rates of 20-30% when treated with high-dose chemotherapy concomitant with reirradiation. This contrasts significantly with chemotherapy alone, which results in essentially no long-term cures. Similarly, the use of radiation alone (without chemotherapy) is conceptually flawed because these patients have failed radiation therapy as a single modality in the past and are therefore considered to have self-selected for a tumor that has arisen from relatively radioresistant clonogenic tumor cells. Despite the potential for long-term cures with high dose chemotherapy and reirradiation, toxicity is significant and outcomes are still relatively poor. The results of reirradiation combined with concomitant chemotherapy represent an improvement over the traditional approaches of surgery alone or chemotherapy alone. These improvements come at the cost of increased toxicity.

It is clear that the overall prognosis remains poor for patients with recurrent head and neck cancer, even after high dose reirradiation and chemotherapy. Novel approaches to enhance the efficacy of radiation therapy with minimal added toxicity are of interest. One such promising method is the use of local intratumoral therapies given concurrently with radiation therapy. The local injection of the biologic agent TNFerade™ biologic avoids the systemic toxicity of the chemotherapy and utilizes locoregionally activated tumor necrosis factor-alpha (TNF-α).

TNFerade™ biologic is an El-, E4-, and partial E3-deleted, replication-deficient adenovirus serotype 5 vector, including the human TNF-α cDNA with a portion of the Egr-1 chemoradiation inducible promoter ligated upstream. The use of TNFerade™ biologic gene transfer therapy provides a strategy that seems particularly appropriate in the context of TNF-a, which has documented potent anti-cancer properties, but high systemic toxicity. In addition, direct injection of the gene into the tumor provides a convenient means of delivery. TNFerade™ biologic has the additional advantage compared to most other anti-cancer gene transfer therapy strategies that it capitalizes on a secreted protein (TNF-α). Consequently, only a certain (presumably small) fraction of the cells within the tumor need to be transfected and secrete the protein.

TNFerade™ biologic is also selected due to its synergy with radiation. Based on previous studies, local administration of TNFerade™ biologic in combination with fractionated external beam radiotherapy can result in increased response rates in solid tumors as compared with radiation therapy alone.

TNFerade™ biologic may enhance the efficacy of chemoradiotherapy for poor prognosis head and neck cancer patients, without significantly increasing locoregional or systemic toxicities. Thereby, the purpose of this study is to assess the safety, tolerability, and "Proof of Concept" of TNFerade™ biologic in combination with concomitant radiotherapy and chemotherapy (5-FU and hydroxyurea) in patients with unresectable recurrent head and neck cancer.

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