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A Pilot Study of Induction Triplet Chemotherapy Followed by Minimally Invasive Surgery for Stage 3-4 Resectable Oropharyngeal Cancer

Krishna Rao[1,2,3,4*], **Kathy Robinson**[4], **James Malone**[4,5], **Cathy Clausen**[6], **Bruce Shevlin**[6] **and K Thomas Robbins**[4,5]

[1]*Department of Internal Medicine, Southern Illinois University School of Medicine, USA*

[2]*Division of Hematology/Oncology, Department of Internal Medicine, Southern Illinois University School of Medicine, USA*

[3]*Department of Medical Microbiology, Southern Illinois University School of Medicine, USA*

[4]*Simmons Cancer Institute at SIU, Southern Illinois University School of Medicine, USA*

[5]*Division of Otolaryngology Head and Neck Surgery, Department of Surgery, Southern Illinois University School of Medicine, USA*

[6]*St. John's Hospital Department of Radiation Oncology, Springfield, IL, Southern Illinois University School of Medicine, USA*

[*]**Corresponding author:** Krishna Rao, Simmons Cancer Institute at Southern Illinois University School of Medicine, 315 W. Carpenter St., PO Box 19678, Springfield, IL 62794-9678, USA, Tel: 2175457045; Fax: 2175457021; E-mail: krao@siumed.edu

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Abstract

The current study reports the results of an open label pilot study evaluating a novel treatment protocol for patients with locally advanced head and neck cancer. Patients received induction chemotherapy and those who had a clinical complete response to induction chemotherapy were offered trans-oral nidusectomy for the primary lesion and neck node dissection. If a pathologic complete response was achieved, patients were then observed. Patients not achieving a clinical or pathologic complete response to induction therapy were subsequently treated with chemoradiation.

Keywords: Induction; Head and neck cancer; Chemotherapy

Introduction

Three modalities of therapy have established roles in the treatment of carcinoma of the head and neck: surgery, radiation therapy, and chemotherapy. The choice of which modality to use depends upon many factors such as the site and extent of the primary lesion, the likelihood of complete surgical resection, the presence of lymph node metastases, and the associated acute and long term toxicities. Traditionally, smaller lesions (stage T1-T2) are effectively treated with surgical excision or irradiation whereas more advanced disease (stage III-IV) is treated with combined surgery and radiation therapy. The use of such combined modality therapy represents an important advancement in the treatment of this disease [1-3]. However, even when surgery and radiation therapy are used concomitantly, only a minority of patients with advanced regional disease are cured; and the subsequent morbidity related to radiation, including xerostomia, dysphonia, and dysphagia, is a major problem among survivors [4].

The use of a third modality, chemotherapy, has provided an additional option for improved survival when combined with radiation therapy. Of particular note is the ECOG trial in which IV cisplatin administered concomitantly with radiation therapy was more effective than radiation alone and equally effective as polychemotherapy combined with split course radiation therapy [5]. Cisplatin has received the greatest attention over the past 2 decades particularly in its combination with 5-fluorouracil.

Whereas the tumoricidal effects of combination regimens may be greater, this potential advantage is partly negated by the higher rates of normal tissue toxicity, particularly if it is combined with radiation therapy.

Chemotherapy's greatest impact has been for locally advanced disease when used in combination with radiation therapy. However, more recent trials using an induction triplet chemotherapy regimen prior to concomitant chemoradiation have demonstrated even better results for local-regional disease control and overall survival. In the TAX 324 study with a minimum of 2 years of follow-up (3 years for 69% of patients), significantly more patients survived in the triplet chemotherapy group versus the doublet chemotherapy group (hazard ratio for death, 0.70; P=0.006). Estimates of overall survival at 3 years were 62% in the triplet group and 48% in the doublet group; the median overall survival was 71 months and 30 months, respectively (P=0.006) [6]. An important observation of the induction triplet chemotherapy regimen is that there was an unprecedented high proportion of patients treated who had a complete response of their disease upon the completion of the induction phase, even before chemoradiation [7]. Despite the improvements in disease control and survival that have been shown with chemoradiation protocols for advanced head and neck cancer, there continues to exist the problem of treatment toxicity and its impact on quality of life. Whereas the major toxic effects of chemotherapy are acute and mostly reversible, the adverse sequelae of radiation therapy are both acute and chronic. Long term effects such as xerostomia, fibrosis, strictures, and soft tissue or bone necrosis can be highly devastating or even morbid [8,9]. The development of an effective treatment protocol that does not rely on radiation therapy would be a major advancement in terms of improving quality of life parameters.

One treatment strategy for patients with advanced head and neck cancer who prove to be highly sensitive to chemotherapy is to combine the modalities of polychemotherapy and conservation surgery 4 with the goal of avoiding radiation therapy. For those patients whose primary disease is classified as T2-3 (resectable), and who have a complete response following induction therapy, it is feasible to

perform an organ preservation tumor nidusectomy at the primary site to verify that the clinical complete response is truly a pathological complete response. Similarly, the clinical complete response observed for the associated nodal disease, can be verified pathologically by performing a selective neck dissection without causing significant morbidity. Both tumor nidusectomy and selective neck dissection has been shown to be an effective adjuvant in this setting. Building on these observations, we conducted a novel protocol in patients with locally advanced head and neck cancer. Patients received induction chemotherapy and those that had a clinical complete response to induction chemotherapy were offered nidusectomy and neck node dissection. If a pathologic complete response was achieved, patients were then observed. Patients not achieving a clinical or pathologic complete response to induction therapy were treated with chemoradiation.

Materials and Methods

This was an open label, non-randomized, pilot study. After obtaining approval from the Springfield Committee for Research Involving Human Subjects (SCHRIS), we proceeded forward with this study. The study was also registered at clinicaltrials.gov and assigned a study number of NCT 01111942. Between May 2006 and May 2010, a total of 4 adult patients were enrolled in the study after obtaining written informed consent. Patients eligible for the study included those with biopsy proven, previously untreated, stage III-IV (T1, T2, T3) (N0-N2) squamous cell carcinoma of the oropharynx staged according to AJCC guidelines. Patients with T4 tumors or N3 neck disease were excluded as were patients with a prior history of malignancy, excluding basal and squamous cell carcinoma of the skin and carcinoma in situ of the cervix. The oropharynx subsite was selected for this trial as tumors in the region are very amenable to surgical access and potential nidusectomy.

Prior to chemotherapy, at the time of examination under anesthesia and panendoscopy, the interface between the soft tissue involvement of the tumor and the surrounding normal mucosa was tattooed with India ink. This served to mark the site of future nidusetomy. All subjects enrolled received induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil. Induction chemotherapy was given over 3 cycles, each cycle consisting of 21 days.

Following induction triplet chemotherapy, subjects were restaged by physical examination and radiological imaging. If there was an unequivocal absence of evidence for residual disease (i.e. an apparent complete response), the subject underwent conservation surgery and neck node dissection under general anesthesia.

Using a transoral approach, the region that was previously involved by the primary tumor was excised. The amount of tissue removed was intended to be minimal and accessed directly without major exposure techniques. The intent of conservation surgery was to remove the residual abnormal (scar) tissue in the region originally occupied by the cancer rather than to perform an oncologic resection in which 1-2 cm margins around the tumor are included. The lymph node groups at risk were removed en bloc based on neck level or sublevel. For subjects with positive nodal disease prior to induction therapy, this included the neck level that was involved and at least one neck level distal to the pattern of flow for the lymphatic drainage. For subjects at risk for bilateral nodal involvement (base of tongue, posterior pharyngeal wall, and soft palate) the levels at risk were also removed. Post-surgery, patients were then carefully monitored for maintenance of disease remission.

All subjects with clinical or radiological evidence of persistent disease and who failed to achieve a clinical complete response to induction triplet chemotherapy as evidenced by physical examination and CT/PET scan subsequently underwent concomitant chemoradiation. Radiation therapy consisted of 6 conventional standard beam or IMRT to the involved areas according to NCCN guidelines at the discretion of the treating physician. Suggested total dosage was 5600 to 7000 Gy. Carboplatin was administered weekly during radiotherapy at an AUC dosage of 1.5.

Quality of life measurements were performed on all patients FACT H and N, UW-QOL,[10] and MDADI questionnaires. Subjects were followed for 24 months after cessation of study treatment, progression of disease with subsequent treatment with a non-study treatment, or until death.

The study protocol permitted enrollment to 10 patients of which at least 1 of the first five needed to achieve a complete clinical and pathologic response to induction TPF therapy in order to continue the study and enter 5 additional patients.

Results

A total of four male patients were enrolled in the study. Enrollment of the fifth patient was elusive due to the rurality of the patient population and long travel distance for protocol based therapy, which potentially included daily radiation treatments.

The age of the patients ranged from 55 to 67, with an average of 60.75 years. Subsites of involvement included the tonsil (50%) and base of tongue (50%). Three patients had T2 lesions while one patient had a T3 lesion. Nodal status ranged from N1 (50%) to N2b (50%). All four patients had HPV positive disease. Characteristics are noted in Tables 1 and 2.

Characteristics	Number or Percent
Enrolled in Study	4
Average Age	60.75
Gender	----
Male	100%
Female	0%
Ethnicity	----
European	100%

Table 1: Patient characteristics.

N1	N2b
T2	1
T3	1

Table 2: Tumor characteristics of patients.

	Mild	Moderate	Severe	Life Threatening	Fatal
Alopecia	100%	3			
Anemia		1			
Anorexia	3	3	2		
Ascites		1			
Atrial Fibrillation		1			
Low Hematocrit		1			
Low RBC		1			
Bands				1	
Bruising	1				
Constipation	2				
Cough	1				
Creatinine Elevated	2	1	1		
Dehydration		2	1		
Diarrhea	3	4	1		
Distention/Bloating of Abdomen		1	1		
Dizziness	1	1			

Table 3: List of toxicities and grading with number of patients exhibiting the toxicity listed in each cell.

One of the four patients received only one cycle of TPF and had to stop due to nephrotoxicity. Of the remaining three who completed protocol therapy, one patient did achieve a complete clinical response and went to surgery. Pathology from the surgery showed evidence of residual carcinoma, and received chemoradiation. The other two patients, not having achieved a clinical complete response, received chemoradiation with weekly carboplatin. All four patients are alive and disease free with over 24 months of follow-up.

Grade 3 or higher toxicities included anorexia (50%), renal failure (25%), dehydration (25%), diarrhea (25%), abdominal distension and bloating (25%), fatigue (25%), hypocalcemia (25%), hypokalemia (50%), hypomagnesemia (25%), hyponatremia (25%), hypophosphatemia (25%), hypotension (25%), infusa-port site infections (75%), insomnia (25%), lymphopenia (25%), anxiety (25%), depression (50%), nausea (50%), neutropenia (75%), neutropenic fever (25%), small bowel obstruction (25%), salivary gland changes (25%), sepsis (25%), thrombosis (25%), and vomiting (50%). Adverse events that were serious i.e. required hospitalization included atrial fibrillation, dehydration, diarrhea, depression, neutropenic fever, nausea, salivary gland changes, sepsis, thrombosis, and vomiting. All toxicities are outlined in Table 3.

Discussion

The role of taxanes and the use of triplet induction chemotherapy in head and neck cancer still remain controversial due to the conflicting results of several randomized studies. Positive studies, which motivated us to perform this present study, include TAX 323 and TAX 324. Initially, Investigators at the Dana Farber Cancer Institute conducted a series of Phase II studies evaluating the addition of docetaxel to PF-based chemotherapy. Consistently, high complete response rates (42%-61%) and overall response rates (91%-100%) were noted [11]. Based on these studies, TAX 324 was conducted [6]. Five hundred and one patients (all of whom had stage III or IV disease with no distant metastases and tumors considered to be non-resectable or were candidates for organ preservation) were randomly assigned to receive either TPF or PF induction chemotherapy, followed by chemoradiotherapy with weekly carboplatin therapy and radiotherapy for 5 days per week. The primary end point was overall survival.

With a minimum of 2 years of follow-up, significantly more patients survived in the TPF group than in the PF group. Estimates of overall survival at 3 years were 62% in the TPF group and 48% in the PF group; the median overall survival was 71 months and 30 months, respectively. There was better locoregional control in the TPF group than in the PF group, but the incidence of distant metastases in the two groups did not differ significantly. The EORTC 24971/ TAX 323 study used a slightly different dosing scheme for the TPF regimen and conducted a similar study. Importantly, the study omitted concurrent chemotherapy with the radiation, and the radiation was delivered either as fractionated or hyperfractionated therapy. A total of 358 patients underwent randomization, with 177 assigned to the TPF group and 181 to the PF group. At a median follow-up of 32.5 months, the median progression-free survival was 11.0 months in the TPF group and 8.2 months in the PF group. Treatment with TPF resulted in a reduction in the risk of death of 27%, with a median overall survival of 18.8 months, as compared with 14.5 months in the PF group. The authors concluded that induction chemotherapy with the addition of docetaxel significantly improved progression-free and overall survival in patients with non-resectable squamous cell carcinoma of the head and neck [12].

Licitra L et al. [13] reported their experience of primary chemotherapy in resectable oral cavity squamous cell carcinoma. Patients were randomized to receive either initial surgery or neoadjuvant (induction) chemotherapy with three cycles of cisplatin and 5-FU followed by surgery. The study noted a pathologic complete response rate of 27% at the primary site after the neoadjuvant chemotherapy. Thirty-three percent of patients had a pathologic complete response or near complete response at both the primary site and regional lymph nodes. Although the addition of neoadjuvant treatment did not impact overall survival, it did have some intriguing effects. “Less demolitive surgery (31% vs 52%)” was required in the surgery arm without an increased rate of positive margins and less postoperative radiotherapy (33% vs 46%) was used. Additionally, Haddad et al. [7] reported the results of pathologic complete responses in head and neck cancer patients treated with triple induction chemotherapy followed by chemoradiation. The study noted that, post TPF induction, primary site biopsy was negative in 89% (64/72) of patients. Neck dissection was performed in patients with N3 disease and those who did not achieve a clinical complete response. Twenty-two of twenty-nine patients (76%) achieved a pathologic complete response post all treatment. Holsinger et al. [14] conducted a study using triple induction chemotherapy with paclitaxel, ifosfamide, and cisplatin (TIP) in patients with stage III and stage IV laryngeal squamous cell carcinoma. Patients received three cycles of TIP. Patients with a partial response received conservation laryngeal surgery while those achieving a complete pathologic response received an additional three cycles of TIP. Thirty-seven percent of patients

achieved a pathologic complete response. Nearly all of those patients (90%) maintained a durable remission. Of the remaining patients, laryngeal preservation was possible in 83% and only 16% of patients required post-operative radiation.

Our own study failed to substantiate the expected pathologic complete response rates of other studies, despite a 100% HPV positivity rate. However, minimally required surgery was performed on one patient who remains in complete remission. Thus, the benefit of neoadjuvant chemotherapy may be the reduction in the performance of functionally impairing surgery. Additionally, as suggested by the Holsinger study, it may be that neoadjuvant chemotherapy and conservative surgery may be as effective as surgery and radiation or chemoradiation in selected head and neck cancer patients. The statistical design of the study was also rigorous. Although the failure to recruit a fifth patient had impaired the original design of the study, we think that these negative results still do remain valid and provide important information for future trial design.

The amount of acute toxicity encountered in our study was high, which made it difficult for patients to complete the three cycles of triplet chemotherapy. Other studies using the triple induction regimen have reported high rates of acute toxicity as well. Schrijvers et al. [15] reported their outcomes and noted diarrhea (70%), stomatitis (65%), nausea (83%), and vomiting (70%) at dose level II of cisplatin (100 mg/m2). Nearly 15% of patients experienced nephrotoxicity. Patients on the DECIDE trial were noted to have grade 3/4 mucositis (50%), dysphagia 12%), and infection (11.2%) [16]. The PARADIGM study, which used a slightly different induction regimen of docetaxel, hydroxyurea, and 5- fluorouracil, noted no difference in rates of mucositis, pain scores, xerostomia, and PEG tube use with patients randomized to receive induction chemotherapy [17]. The intriguing benefit of induction chemotherapy may, in fact, be the reduction in subsequent radiation intensity in the HPV positive setting. The Phase II ECOG 1308 study enrolled HPV positive patients and treated them with a three cycle induction regimen of carboplatin, paclitaxel, and cetuximab followed by chemoradiation with weekly cetuximab and reduced dose intensity modulated radiation therapy (IMRT) of 54 Gy, if the patient had achieved a clinical complete response after induction chemotherapy. Late toxicities were minimal, and the results in this group of patients were excellent with an 84% progression free survival at 23 months and a 95% two year survival. We believe that the toxic effects of induction chemotherapy, both short term and long term, should not be underestimated and thorough patient counseling is necessary prior to activating such a treatment approach.

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