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CLINICAL INVESTIGATION **Head and Neck**

PHASE II TRIAL OF HYPERFRACTIONATED INTENSITY-MODULATED RADIATION THERAPY AND CONCURRENT WEEKLY CISPLATIN FOR STAGE III AND IVa HEAD-AND-NECK CANCER

PATRICK D. MAGUIRE, M.D.,* MICHAEL PAPAGIKOS, M.D.,* SUE HAMANN, PH.D.,† CHARLES NEAL, M.D.,* MARTIN MEYERSON, M.D.,* NEIL HAYES, M.D.,‡ PETER UNGARO, M.D.,§ KENNETH KOTZ, M.D.,§ MARION COUCH, M.D.,‖ HOKE POLLOCK, M.D.,¶ AND JOEL TEPPER, M.D.#

Departments of *Radiation Oncology, §Medicine, ¶Surgery, and †Coastal Area Health Education Center, New Hanover Regional Medical Center, Wilmington, NC; and Departments of #Radiation Oncology, ‡Medicine, and ‖Surgery, University of North Carolina Hospitals, Chapel Hill, NC

Purpose: To investigate a novel chemoradiation regimen designed to maximize locoregional control (LRC) and minimize toxicity for patients with advanced head-and-neck squamous cell carcinoma (HNSCC).

Methods and Materials: Patients received hyperfractionated intensity modulated radiation therapy (HIMRT) in 1.25-Gy fractions b.i.d. to 70 Gy to high-risk planning target volume (PTV). Intermediate and low-risk PTVs received 60 Gy and 50 Gy, at 1.07, and 0.89 Gy per fraction, respectively. Concurrent cisplatin 33 mg/m^2/week was started Week 1. Patients completed the Quality of Life Radiation Therapy Instrument pretreatment (PRE), at end of treatment (EOT), and at 1, 3, 6, 9, and 12 months. Overall survival (OS), progression-free (PFS), LRC, and toxicities were assessed.

Results: Of 39 patients, 30 (77%) were alive without disease at median follow-up of 37.5 months. Actuarial 3-year OS, PFS, and LRC were 80%, 82%, and 87%, respectively. No failures occurred in the electively irradiated neck and there were no isolated neck failures. Head and neck QOL was significantly worse in 18 of 35 patients (51%): mean 7.8 PRE vs. 3.9 EOT. By month 1, H&N QOL returned near baseline (mean 6.2, SD = 1.7). The most common acute Grade 3+ toxicities were mucositis (38%), fatigue (28%), dysphagia (28%), and leukopenia (26%).

Conclusions: Hyperfractionated IMRT with low-dose weekly cisplatin resulted in good LRC with acceptable toxicity and QOL. Lack of elective nodal failures despite very low dose per fraction has led to an attempt to further minimize toxicity by reducing elective nodal doses in our subsequent protocol.

Hyperfractionation, IMRT, Chemoradiation, Head-and-neck cancer.

INTRODUCTION

Chemoradiation (CRT) has become the standard of care for most patients with locally advanced head-and-neck squamous cell cancer (HNSCC). Multiple Phase III trials and two meta-analyses have shown significantly improved locoregional control (LRC) with CRT over radiotherapy alone, with at least two showing an overall survival (OS) benefit as well (1–6). Altered fractionation schemes including accelerated and hyperfractionated radiation therapy (AFRT) have also shown benefits over standard fractionation (7–9). Unfortunately, the improved efficacy that results from either CRT or AFRT comes at the price of higher rates of treatment-related toxicity. Both CRT and AFRT increase the risk of acute severe mucositis and skin toxicity compared with RT alone. Long-term toxicities of xerostomia and swallowing dysfunction are also major problems with these regimens.

Although AFRT or CRT result in higher efficacy and toxicity compared with conventionally fractionated RT alone, it remains to be proved whether incorporating AFRT into CRT regimens has any additive or synergistic effect. Does CRT that incorporates AFRT improve survival over conventionally fractionated CRT? Are these regimens associated with acceptable toxicity? These topics were addressed in the Radiation Therapy Oncology Group (RTOG) 0129 Phase III trial, which has closed to accrual but has not been reported. In the meantime, the current standard CRT arm for the ongoing RTOG 0522 trial uses AFRT via concomitant boost technique, one of the ''winning'' arms of RTOG 90-03, delivered with concurrent cisplatin at 100 mg/m^2 on Days 1 and 21.

Reprint requests to: Patrick D. Maguire, M.D., New Hanover Radiation Oncology, 1988 S. 16th Street, Wilmington, NC 28401; Tel: (910) 251-1839; Fax: (910) 251-8286; E-mail: pmaguire@nhroc.com

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Our institutional CRT standard for patients with locally advanced HNSCC at New Hanover Regional Medical Center differs from that of the RTOG.

In 1998, the group at Duke University published their Phase III trial testing hyperfractionated RT alone vs. AFRT at 1.25 Gy twice daily to 70 Gy with concurrent cisplatin and fluorouracil (10). Chemotherapy was delivered in the hospital during Weeks 1 and 5. In this study, CRT resulted in significantly improved LRC and progression-free survival (PFS) with a trend toward improved OS. Previously, we reported our results in the community setting using this CRT regimen in 50 patients with Stage III and IVa HNCCC (11). Although 2-year actuarial OS was 80%, significant toxicities were recorded including 100% Grade 3 acute mucositis and 14% chronic pharyngeal stricture at a median follow-up of 23 months. Xerostomia was also a common long-term complaint for these patients who were treated without the potential benefit of intensity-modulated radiation therapy (IMRT). In sum, this intensive regimen was highly efficacious but toxic.

In designing the new CRT protocol reported here, the authors hoped to maintain high rates of LRC and survival while minimizing toxicity and any negative impact on QOL in three ways. First, intensity modulation was incorporated into the accelerated, hyperfractionated RT (HIMRT) in an attempt to decrease to the volume of nontarget tissues within the RT field. Second, a nonstandard, very low dose per fraction was selected to be delivered to both intermediate and low-risk PTVs. Third, the chemotherapy regimen was altered by eliminating 5-fluorouracil and changing concurrent cisplatin dose to 33 mg/m^2 delivered weekly. The current report is, to our knowledge, the only study in the medical literature that has combined these components of weekly cisplatin without 5FU, IMRT, and low radiation dose per fraction given twice daily for treatment of patients with HNSCC. The purpose of this study was to evaluate the QOL, efficacy, and toxicity associated with this novel CRT regimen.

METHODS AND MATERIALS

Patient eligibility

Adults with newly diagnosed, biopsy-proven stage III and IVa squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx were eligible. In order to minimize the risk of underdosing target tissues with parotid-sparing IMRT planning, patients with stage N2c and N3 neck disease were ineligible. Patients with nasopharynx and unknown primary carcinomas were excluded. Patients were also ineligible if they had prior head and neck radiation therapy, prior chemotherapy, other invasive malignancies (excluding nonmelanoma skin cancer) within the last 5 years, or symptomatic heart disease within the past 6 months. Other eligibility criteria included Eastern Cooperative Oncology Group performance status of 0 or 1, absolute neutrophil count greater than 1.5×10^9/l, platelet count greater than 100×10^9/l, bilirubin less than 1.5 mg/dl, and serum creatinine less than 1.5 mg/dl. The study was opened at New Hanover Regional Medical Center (NHRMC) in Wilmington, NC, in August 2004. In January 2007, the study was opened for enrollment to patients at the University of North Carolina Hospital in Chapel Hill, NC. The study was approved by institutional review boards at both institutions. In addition, a Data and Safety Monitoring Board at NHRMC provided independent oversight for the trial. Each patient gave written informed consent before enrollment.

Pretreatment evaluation

All patients were evaluated by otolaryngology, radiation oncology, medical oncology, oral surgery, and nutrition services. Laboratory evaluation consisted of complete blood count, electrolytes, magnesium, creatinine, total protein, pre-albumin, alkaline phosphatase, total bilirubin, AST, and ALT. Staging included neck computed tomography (CT), barium swallow, and chest X-ray before treatment. Positron emission tomography (PET)/CT was optional.

Radiation therapy

Immobilization for RT planning was via an Accufix device to ensure minimal in-field motion during simulation and treatment. The CT planning was performed with 3-mm axial images obtained from the top of the head through the top of the aortic arch. The PET/CT data sets were imported for image fusion planning at the discretion of the treating physician.

General definitions of gross tumor volume, clinical target volume, and planning target volume were according to ICRU report 50. Hyperfractionated radiation therapy was administered using intensity modulation (HIMRT) in fractions of 1.25 Gy delivered twice daily, 5 days per week, to a total dose of 70 Gy to the high-risk planning target volume (PTV70). Intermediate and low-risk target volumes in the neck received 60 Gy (PTV60) and 50 Gy (PTV50) at 1.07 and 0.89 Gy per fraction, respectively. A single treatment plan was used. A separate anterior supraclavicular field with central blocking over the larynx was used to treat the low neck whenever possible (generally for all primary disease sites other than hypopharynx or larynx). The conformal supraclavicular field was treated to 44 Gy at 2 Gy per fraction, matched to the primary IMRT fields using a common isocenter technique.

Chemotherapy

Patients received cisplatin 33 mg/m^2 i.v. infusion, at a rate of 1 mg/min once weekly during the course of HIMRT, started during Week 1. Six total weekly cycles were planned. Delivery of a seventh cycle was optional during the final half week of HIMRT, at the discretion of the treating medical oncologist. Standard hydration measures and premedications were used to prevent significant nausea, vomiting, and/or renal insufficiency.

Quality of life assessment

The Quality of Life Radiation Therapy Instrument (QOL-RTI), a validated QOL questionnaire, consisted of 39 questions, including the head-and-neck module (12, 13). Of these, 24 questions were general QOL, one overall, and 14 head-and-neck specific, of which two specifically addressed swallowing function. Potential responses to all questions were presented on an 11-point Likert-type scale, ranging from 0 (''not at all'') to 10 (''very much so''). Most questions were scored with 10 as positive, where a higher score equates to a better QOL. However, several negatively worded questions were scored by subtracting the response from 10. Patients completed the questionnaire pretreatment (PRE), at end of treatment (EOT), and at 1 month (M01), 3 months (M03), 6 months (M06), 9 months (M09), and 12 months (M012) after completion of CRT.

Statistical analysis

The primary design was a single-group, single-intervention study using a convenience sample of up to 40 consecutive patients over a 36-month period. The primary hypothesis was that reduction in