Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 3, pp. 717–724, 2005

0360-3016/05/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2005.03.001

CLINICAL INVESTIGATION **Head and Neck**

A PHASE I/II STUDY OF NEOADJUVANT CHEMOTHERAPY FOLLOWED BY RADIATION WITH BOOST CHEMOTHERAPY FOR ADVANCED T-STAGE NASOPHARYNGEAL CARCINOMA

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Purpose: Local recurrence is the most common site of failure for locally advanced nasopharyngeal carcinoma (NPC) treated with neoadjuvant cisplatin/5-fluorouracil (PF) and definitive radiation at our center. Based on this, we studied the addition of chemotherapy during the boost phase of radiation after neoadjuvant PF for advanced T-stage (T3–T4) NPC. This strategy was based on theoretical radiosensitization with chemotherapy during accelerated repopulation of the tumor with relatively radioresistant clonogens.

Methods and Materials: Three cycles of neoadjuvant PF was followed by conventionally fractionated radiation with additional PF during the boost portion of the radiation course. An initial Phase I study was done to establish the maximum tolerated dose of concurrent PF.

Results: Forty-four patients were enrolled. Six patients in Phase I defined the MTD for concurrent PF as: cisplatin 10 mg/m^2/day and PF 320 mg/m^2/day, on Days 1–5 during Weeks 6 and 7 of radiation therapy based on dose-limiting toxicities of mucositis, neutropenia, and thrombocytopenia. Forty-one patients were treated with concurrent therapy per protocol: complete, partial, and minor responses were seen in 23, 16, and 2 patients, respectively. Progression-free and overall survival rates at 5 years were 55% (95% CI, 41–75%) and 66% (95% CI, 52–85%), respectively. Seven of 11 tumor-related deaths were due to local recurrence. Nine of 10 patients with local recurrence had T4-stage disease at presentation. Local control of T4 disease was achieved in 74% of patients overall, and in 25% (1/4) with World Health Organization (WHO) type 1, 76% (16/21) with WHO type 2, and 90% (9/10) with WHO type 3 histology. Common toxicities included mucositis, dermatitis, fatigue, vomiting, and weight loss.

Conclusions: This regimen was feasible and associated with promising overall survival. Local recurrence remains the major reason for treatment failure in advanced T-stage NPC, especially WHO types 1 and 2. Other strategies to improve local control in these patients should be investigated. **© 2005 Elsevier Inc.**

Nasopharyngeal carcinoma, Concurrent chemoradiation, Boost chemotherapy.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is distinct from other squamous cell carcinomas of the head and neck (SCCHN) in its epidemiology, presentation, and clinical management. Although rare in the United States, NPC is endemic in areas such as Southern China and Southeast Asia where it is not associated with alcohol or tobacco use. Compared with other mucosal primary tumors in the head and neck, NPC is more frequently associated with advanced nodal disease at presentation, which is correlated with increased risk of distant recurrence (1). NPC is also distinguished by relative chemosensitivity and radiosensitivity. Owing to this radiosensitivity and its relatively inaccessible location, primary tumors of NPC are rarely resected. Surgery is generally reserved for management of refractory or recurrent cervical lymph node involvement or low-volume local recurrence confined to the nasopharynx. Early-stage NPC has been treated successfully with radiation alone. In locally advanced disease, although radiation results in high complete response rates, recurrence is frequent (2). In a retrospective review of 378 patients (75% Caucasian) treated with radiation alone at The University of Texas M. D. Anderson Cancer Center between 1954 and 1992, actuarial survival rates at 5, 10, and 20 years were 48%, 34%, and 18%,

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Supported by The University of Texas M. D. Anderson Cancer Center Physician Scientist Program (F.M.J.).

Received Nov 11, 2004, and in revised form Mar 3, 2005. Accepted for publication Mar 7, 2005.

respectively. Overall, 27% of patients developed distant metastases and 49% of patients died of NPC (1). In that series, advanced T stage was associated with decreased local control and recurrence but not distant metastasis.

When we designed the current trial, the Intergroup 0099 study (3) was in progress, and treatment for advanced stage NPC at our institution was based on a Phase II study published by Dimery *et al.* (4), in which patients with locally advanced disease received three cycles of neoadjuvant cisplatin and PF before definitive radiation therapy. This resulted in 80%, 72%, and 67% overall survival rates at 2, 4, and 6 years, respectively. In that trial, the major cause of failure was persistent or recurrent local disease. Subsequently, in a retrospective cohort analysis of patients treated at the M. D. Anderson Cancer Center on the trial mentioned previously or off-study with a similar approach were matched with patients treated with radiation alone (5). The results of this analysis showed an impact on disease-free and overall survival with the addition of neoadjuvant chemotherapy. For patients with advanced T-stage disease, local recurrence was the most common cause of treatment failure.

To improve local control for patients with advanced T-stage NPC, we studied the addition of chemotherapy during the last 2 weeks of radiation to the standard neoadjuvant PF plus radiation program. The rationale for this approach evolved from previous studies using accelerated fractionation at the end of the radiation treatment schedule (concomitant boost radiation) in patients with SCCHN (6, 7). Theoretically, the improvement in tumor control with concomitant boost radiation accrues from intensification of radiation during the time of accelerated repopulation with relatively radioresistant clonogens. Although the biology of SCCHN is distinct from that of NPC, its increased sensitivity to radiation suggests that this approach could be effective in enhancing local control of NPC as well. In Radiation Therapy Oncology Group Study 90-03, this schedule were more effective in locoregional control relative to conventional fractionation (7). At the time that the study described herein was being planned, we were completing accrual to a Phase II trial of "radiation with chemotherapy boost," a variation on concomitant boost radiation, in patients with locoregionally advanced SCCHN (8). In this approach, concurrent chemotherapy is used to intensify treatment in the last 2 weeks (10 fractions) of the radiation course when the field size has been reduced to boost the gross disease (i.e., the boost portion of radiation). Our positive results in that trial led us to study this form of chemoradiation in patients with advanced T-stage NPC to improve local control.

In the current study, patients received three cycles of PF followed by an additional low dose daily of PF during the boost portion of radiation therapy. Because our prior experience with this regimen did not include the use of neoadjuvant chemotherapy, we performed an initial Phase I study to define the maximum tolerated dose (MTD) of the concurrent PF.

PATIENTS AND METHODS

Patient eligibility and evaluation

Patients with histologically proven NPC Stage T3–4, any N, or M0 disease were eligible for this study. All patients were staged according to the American Joint Committee on Cancer (AJCC) staging system from 1992 (9). Criteria for inclusion in the study included at least 1 bidimensionally measurable lesion, no prior chemotherapy, age $\geq$18 years, a performance status of $\leq$2 (Zubrod), an absolute granulocyte count of $\geq$1500/μL, a platelet count of $\geq$100,000/μL, a serum creatinine level of $\leq$1.5 mg/dL, and a creatinine clearance of $\geq$60 mL/min. Patients were excluded for any prior malignancy except for adequately treated basal or squamous cell skin cancer, *in situ* cervical cancer, or other cancer for which the patient had been disease-free for more than 5 years. Pregnant or breast-feeding women were excluded. Patients who had received previous radiation therapy to the head and neck, except for treatment of nonmelanoma skin cancers outside of the current radiation therapy treatment volumes, were not eligible. Patients were informed of the investigational nature of this study and gave written informed consent in accordance with institutional and federal guidelines. The study was fully reviewed and approved by the Institutional Review Board of The University of Texas M. D. Anderson Cancer Center.

Pretreatment evaluation included a detailed medical history, physical examination, and an evaluation of performance status. A fiberoptic examination of the upper aerodigestive tract including the nasopharynx, oropharynx, hypopharynx, and larynx was performed. A chest X-ray and computed tomography (CT) or magnetic resonance imaging (MRI) scan of the head and neck including the cervical and supraclavicular lymph node–bearing regions were done within 3 weeks of study entry. A CT of the abdomen was done if liver enzymes or bilirubin levels were elevated. Bone scan was performed for elevated alkaline phosphatase. All patients had tests performed before enrollment that included a complete blood count with differential (CBC), platelets, albumin, calcium, electrolytes, blood urea nitrogen, creatinine, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), aspartate aminotransferase (SGOT [or AST]), and a pregnancy test when appropriate. Before being entered in the study, patients were examined by a multidisciplinary team that included medical, surgical, radiation oncology, and oncologic dentistry. Dental extractions deemed necessary were performed, and a prophylactic fluoride treatment program was initiated before radiation therapy.

Neoadjuvant chemotherapy treatment plan and dose modifications

The neoadjuvant chemotherapy consisted of cisplatin intravenously on Day 1 followed by PF by continuous iv infusion. The dose levels are given in Table 1. Three cycles were administered every 3 weeks. All patients started at dose level 0.

A CBC, platelet count, electrolytes, magnesium, blood urea nitrogen, creatinine, alkaline phosphatase, LDH, SGPT, and total

Table 1. Dose levels for neoadjuvant chemotherapy

	−1	0
Cisplatin	80 mg/m^2; day 1 only	100 mg/m^2; day 1 only
5-FU	1000 mg/m^2/day; days 1–4	1000 mg/m^2/day; days 1–5