

CONCURRENT WEEKLY DOCETAXEL AND CONCOMITANT BOOST RADIATION THERAPY IN THE TREATMENT OF LOCALLY ADVANCED SQUAMOUS CELL CANCER OF THE HEAD AND NECK

ROY B. TISHLER, M.D., PH.D.,* MARSHALL R. POSNER, M.D.,† CHARLES M. NORRIS, JR., M.D.,‡
ANAND MAHADEVAN, M.D.,§ CHRISTOPHER SULLIVAN, M.D.,‡ LAURA GOGUEN, M.D.,‡
LORI J. WIRTH, M.D.,† ROSEMARY COSTELLO, R.N.,† MARYANN CASE, R.N.,† SARA STOWELL, B.S.,†
DAN SAMMARTINO, B.S.,† PAUL M. BUSSE, M.D., PH.D.,§ AND ROBERT I. HADDAD, M.D.†

*Department of Radiation Oncology, Dana Farber Cancer Institute, Brigham and Women's Hospital, Boston, MA; †Department of Medical Oncology, Dana Farber Cancer Institute, Brigham and Women's Hospital, Boston, MA; ‡Department of Surgery, Brigham and Women's Hospital, Boston, MA; §Department of Radiation Oncology, Beth Israel Deaconess Medical Center, Boston, MA

Purpose: In a Phase I/II trial, we investigated concurrent weekly docetaxel and concomitant boost radiation in patients with locally advanced squamous cell cancer of the head and neck (SCCHN) after induction chemotherapy. **Patients and Methods:** Patients presented with American Joint Committee on Cancer Stage III/IV and were treated initially with induction chemotherapy using cisplatin/5-fluorouracil (PF), carboplatin-5-FU, or docetaxel-PF. Patients then received docetaxel four times weekly with concomitant boost (CB) radiation (1.8 Gy once-daily X20, 1.8/1.5 Gy twice a day). Fifteen patients each received 20 mg/M² and 25 mg/M².

Results: Thirty-one patients were enrolled and 30 were evaluable for response and toxicity. Median follow-up was 42 months (range, 27–63 months). Primary sites were: oropharynx 19, oral cavity 2, larynx/hypopharynx 5, and unknown primary 4. Eighty-seven percent of patients had N2/N3 disease; 60% had T3/T4 disease. Twenty percent of patients had a complete response (CR) to induction chemotherapy. After chemoradiotherapy, 21 of 30 patients had a CR, 2 had progressive disease, and 7 had partial response (PR). Nineteen of 26 patients presenting with neck disease had neck dissections, and 7 of 19 were positive. Ninety-three percent of all patients were rendered disease-free after all planned therapy. Treatment failed in 8 patients, and 7 have died of disease. An additional patient died with no evidence of disease. Twenty-one patients (70%) are currently alive with no evidence of disease. No acute dose-limiting toxicity was observed at either dose level.

Conclusions: This intensive treatment regimen of concurrent docetaxel/concomitant boost radiation and surgery after induction chemotherapy in poor prognosis patients yields good local regional control and survival. Docetaxel/CB chemoradiotherapy represents an aggressive alternative regimen to platinum-based chemoradiotherapy or surgery in patients who have a poor response to induction chemotherapy. © 2006 Elsevier Inc.

Head-and-neck cancer, Chemoradiation, Concomitant boost radiation, Docetaxel.

INTRODUCTION

The optimal combination of agents for nonsurgical local-regional therapy of advanced squamous cell cancer of the head and neck (SCCHN) remains controversial. Once daily external-beam radiation therapy (standard fractionated, SF) has been the standard of care for many years and has served as the basic framework for two distinct and promising approaches, which have demonstrated an improvement in outcomes. The strategies that have evolved independently

are altered fractionation radiation and concurrent chemoradiotherapy. Studies examining altered radiation schedules (both hyperfractionation and accelerated fractionation [AF]) have shown improved local control compared with SF, defined as once-daily radiation fractions of 1.8–2.0 Gy delivered to a total dose of ~70 Gy (1–4). A multi-institutional Phase III study (Radiation Therapy Oncology Group [RTOG] 90-03) compared SF radiation with three altered fractionated radiation schedules (5). Two of the altered fractionation schedules resulted in significantly improved

Reprint requests to: Roy B. Tishler, M.D., Ph.D., Department of Radiation Oncology, Dana Farber Cancer Institute, 44 Binney St., Boston, MA 02115. Tel: (617) 632-3591; Fax: (617) 632-4247; E-mail: roy_tishler@dfci.harvard.edu

Paul M. Busse, M.D., Ph.D., is currently at the Department of Radiation Medicine, Massachusetts General Hospital, Boston, MA.

Presented in part at the American Society of Clinical Oncology

Annual Meeting, New Orleans, LA, June 2004; Chicago, IL, June 2003; and at the European Society for Medical Oncology Annual Meeting, Nice, France, October 2002.

Supported in part by a clinical research grant from Aventis (Sanofi).

Received Dec 10, 2005, and in revised form Feb 5, 2006. Accepted for publication Feb 6, 2006.

local-regional control. One of these two regimens is the accelerated fractionation concomitant boost (AF/CB; 1.8/1.5 Gy with 12 days of twice daily, total dose = 72.0 Gy), which is now considered a standard for locally advanced SCCHN and is incorporated into our combined modality treatment plan.

In parallel with improvement of local-regional control derived from modified radiation schedules, many studies demonstrate the benefit of concurrent chemoradiotherapy. These programs typically consist of a systemic agent delivered with standard fractionated radiation. Many drugs, including 5-fluorouracil (5-FU), cisplatin, hydroxyurea, and carboplatin, have shown increased local-regional control in Phase II trials when added to standard fractionated radiation, compared with expected outcomes with radiation alone, although survival advantages have been harder to demonstrate (6–10). Most definitive Phase III (e.g., RTOG 91-11 [11]) studies have focused on cisplatin alone or 5-FU in combination with either cisplatin or carboplatin, as these are among the most effective chemotherapeutic agents in SCCHN (12, 13). The taxanes (paclitaxel, docetaxel) have also attracted significant interest in combination with radiation, based on preclinical data showing a beneficial effect of the drugs as radiosensitizing agents (14–16) and Phase I/II clinical trials (17–20). In addition to determining the best combination of drugs and radiation for local-regional control, identifying the optimal sequence of radiation and chemotherapy for advanced SCCHN remains an active research topic. Both randomized studies and meta-analysis have demonstrated a benefit for concurrent chemoradiotherapy (21). In addition, meta-analysis has demonstrated a small, but significant benefit for the subset of induction patients receiving a platin-5-FU-based regimen (21). Previously, in induction chemotherapy-based studies, patients received standard fractionated radiation therapy for local-regional treatment after an induction regimen of 2–4 cycles of chemotherapy (22–25). Recent Phase II and III trials, however, have combined more aggressive local-regional therapy by following cisplatin/5-fluorouracil-based induction chemotherapy with chemoradiotherapy in an attempt to maximize the overall therapy (19, 26, 27). Using this sequential therapy model, clinicians have the ability to adjust the intensity and toxicity of the subsequent local-regional therapy, based on the response to the induction chemotherapy (27).

In the current study, we investigated an aggressive local-regional chemoradiotherapy approach in patients treated with induction chemotherapy. The population treated in our trial consisted of SCCHN patients with advanced disease who initially had a course of cisplatin/5-fluorouracil-based induction chemotherapy and, in most cases, had a poor response to the induction therapy. The Phase I/II trial consisted of an AF/CB radiation schedule with weekly docetaxel given during the first 4 weeks of once-daily radiation. In total, 30 patients were treated with a weekly docetaxel dose of 20 or 25 mg/M² and monitored for response, survival, and toxicity.

PATIENTS AND METHODS

All patients were seen in a multidisciplinary clinic where they received initial evaluations and treatment recommendations by a team of radiation oncologists, medical oncologists, and head-and-neck surgeons. Patients had biopsy-proven Stage III or IV (M0) SCCHN and had not received chemotherapy or radiation therapy previously for another SCCHN. Patients were eligible for this trial if they had undergone from one to three courses of a platinum/5-FU-based induction chemotherapy regimen, which could also include a taxane. Patients entered on this trial tended to be those considered at high risk for relapse after induction chemotherapy (less than a complete response [CR] in the neck or primary site), but this was not an absolute entry requirement. Eligible patients signed an Institutional Review Board-approved informed consent before trial entry. Patients were required to be >18 years of age, have an Eastern Cooperative Oncology Group performance status of ≤2, and be taking in adequate nutrition, i.e., not percutaneous endoscopic gastrostomy (PEG) dependent, at the initiation of therapy. Laboratory requirements for protocol entry were: normal bilirubin, serum glutamic oxaloacetic transaminase <1.5 times upper limits of normal, and an alkaline phosphatase <2.5 times upper limits of normal. Hematologic requirements were for a white blood cell count >3,000, absolute neutrophil count (ANC) >1,000, platelets >100,000, and hemoglobin >10 mg/dL.

The initial status of disease was determined by physical examination and radiographic imaging that was obtained within 28 days of entering the trial. Whenever possible, an examination under anesthesia and biopsy were performed to establish the presence of residual disease and staging information after induction chemotherapy but before local-regional treatment. All patients had a PEG tube placed after induction chemotherapy and before initiating combined chemoradiotherapy.

The planned protocol treatment included radiation therapy delivered at a dose of 1.8 Gy/day for 20 treatment days, followed by 11 days of twice-daily radiation using a 1.8-Gy morning dose and a 1.5-Gy afternoon dose with a minimum of 6 h between doses. The total dose was planned to be 72.3 Gy. The initial dose level (arm 1) of docetaxel was 20 mg/M² given weekly, during the first 4 weeks of radiation, which consisted of 1.8 Gy delivered once daily. The second dose level (arm 2) was 25 mg/M² per week. The initial plan was to assess acute toxicity in 3 patients treated at 20 mg/M², and then increase the dose to 25 mg/M² in the remaining patients. Docetaxel was delivered via intravenous infusion such that in a given week the patients received a minimum of three radiation treatments after chemotherapy. Premedications for docetaxel included dexamethasone (10 mg intravenously), diphenhydramine (25 mg intravenously), and ranitidine (50 mg) or cimetidine (300 mg intravenously) given one-half hour before docetaxel infusion. Dexamethasone was also given after drug infusion (10 mg intravenously or orally).

External-beam radiation was typically delivered using a standard three-field technique, consisting of two lateral fields and a supraclavicular field. Intensity-modulated radiation therapy was not used in this study. Fields were required to encompass all disease present at the initiation of therapy. Patients were regularly monitored during therapy. Monthly posttreatment follow-up was carried out in the multidisciplinary clinic with history, physical (including nasopharyngoscopy), and cross-sectional imaging as necessary. Follow-up and time to failure interval were both defined starting from the beginning of chemoradiotherapy.

The plan for neck dissection was based on the nodal response to the induction chemotherapy. If patients had N3 disease or less than a CR in the neck after induction chemotherapy, they were planned to have a neck dissection after the completion of docetaxel/radiation, regardless of the response in the neck at the completion of radiation therapy. If patients presented with an N0 neck, or presented with N1 or N2 disease and had a CR in the neck to induction chemotherapy, a neck dissection was not planned.

A CR was defined as the absence of tumor on physical examination. A partial response (PR) was defined as a decrease of >50% in the product of the two greatest perpendicular dimensions of a lesion, either a lymph node or a primary tumor, on physical examination. A response less than a PR was defined as no response; this includes both stable disease and progressive disease. Tumor primary site and neck were scored separately and combined for overall response assessment. Imaging was used as an adjunct, but was secondary in defining response. Progression-free survival and overall survival were defined as the intervals from initiation of protocol therapy (concurrent chemoradiotherapy) to the most recent follow-up, time of recurrence, or time of death. Dose-limiting toxicities were defined for both hematologic and local-regional parameter. Dose-limiting toxicity was defined for neutropenia (ANC <500/mm³ for >7 days with granulocyte colony-stimulating factor), thrombocytopenia (<20,000/mm³ for >7 days), Grade 3 or greater neurotoxicity, a white blood cell count <3,000, ANC <1,500 or platelets <100,000 for 14 days despite granulocyte colony-stimulating factor, Grade 4 skin/mucosal toxicity or any other toxicity requiring a 14-day or greater radiation break in aggregate, or drug toxicity requiring a greater than 2-week delay in docetaxel administration.

RESULTS

Patient population

A total of 31 patients were entered in the trial from July 2000 to May 2003, and 30 received treatment according to

Table 1. Patient characteristics

Number of patients enrolled	31
Number of patients evaluable	30
Treatment arm distribution	
Arm 1	15 patients
Arm 2	15 patients
Gender	24 men, 6 women
Median age (range)	55.7 (30–77.6)
Cycles of chemotherapy	3 cycles–28 patients 2 cycles–1 patient 1 cycle–1 patient
Induction chemotherapy regimens	
Cisplatin-5-FU	12 patients
Docetaxel, cisplatin-5-FU	11 patients
Carboplatin-5-FU	5 patients
PF/TPF	1 patient
PF/CarboFU	1 patient
Primary site	
Oropharynx	19 patients
Oral cavity	2 patients
Unknown primary	4 patients
Larynx	4 patients
Hypopharynx	1 patient

Abbreviations: 5-FU = 5-fluorouracil; PF = cisplatin/5-fluorouracil; TPF = docetaxel-PF; CarboFU = carboplatinum/5-FU.

Table 2. T, N staging of patient population

	Tx	T1	T2	T3	T4
N0				2	2
N1					
N2	2	1	3	4	8
N3	2		4	2	

N2 + N3 = 86.7% (26/30).

T3 + T4 = 60% (18/30).

the prescribed treatment plan. One patient became ineligible after enrolling, but before starting concurrent docetaxel-radiation, and was excluded; all analysis and discussion was performed on the group of 30 evaluable patients. The characteristics of the patient population are described in Table 1. The median age is 56 years, the majority of the patients are men, and in most cases the primary site was oropharynx (63%). Table 2 illustrates the TN stage of the patients at the time of initial presentation, before receiving induction chemotherapy. All patients were either American Joint Committee on Cancer Stage III (7%) or IV (93%). A high percentage of patients had advanced-stage nodal disease at presentation (87% N2/N3, 13% N0), the majority had advanced T stage (60% T3/T4 disease), and all patients were M0. Pathology for all patients was squamous cell cancer or one of its variants.

All patients received one to three cycles of induction chemotherapy before chemoradiotherapy. As shown in Table 1, 93% of the patients received a full three cycles of induction chemotherapy; 3% received a single cycle and 3% two cycles. Patients received cisplatin/5-FU ($n = 12$), docetaxel/cisplatin/5-FU ($n = 11$), carboplatin/5-FU ($n = 5$), or a combination of two regimens ($n = 2$). The responses to induction chemotherapy and before chemoradiotherapy are summarized in Table 3. The table shows the clinical status of the patients before trial entry. Overall, 24 of 30 patients fit into what could be considered a “poor prognosis” group, in that they achieved less than a CR to induction chemotherapy at either the primary site or in the neck.

Whenever possible, patients with an identified primary site had an examination under anesthesia with primary site biopsy after induction chemotherapy and before trial entry. Of the 26 patients with a primary site, 21 underwent biopsy. Six patients had positive biopsies. Three patients were grossly positive or had computed tomographic evidence of disease and were not biopsied. Thus, 9 of 26 patients had a positive primary site and all 9 patients were clinically PR or had progressive disease at the primary site. There was no intervention performed on the neck at this time other than assessing nodal status as mandated by the protocol.

Response and survival

The median follow-up was 42 months with a range of 27–63 months. The median follow-up for arm 1 was 31

Table 3. Response to induction chemotherapy: fractional response (percentage)

	CR	PR	SD	PD	RR
Primary site	17/26 (65.4)	8/26 (30.8)	—	1/26 (3.8)	25/26 (96.2)
Lymph nodes	5/26 (19.2)	17/26 (65.4)	4/26 (15.4)	—	22/26 (84.6)
Overall	6/30 (20.0)	19/30 (63.3)	4/30 (13.3)	1/30 (3.3)	25/30 (83.3)

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; RR = overall relative response (CR + PR).

Response to induction chemotherapy for the entire patient population, reported separately for primary and nodal sites.

months with a range of 27–63, while for arm 2 it was 47 months with a range of 41–61 months.

The clinical status of patients after chemoradiotherapy is presented in Table 4. Overall, 21 of 30 (70%) patients were completely disease-free after completion of drug-radiation therapy, before planned neck surgery. One patient each had primary site stable disease or progressive disease, and a total of 7 patients had persistent nodal disease. Unfortunately, both patients who did not achieve at least a PR at the primary site died at 6 and 9 months of persistent disease.

For those patients with neck disease remaining after induction chemotherapy, further therapy was indicated. A postchemoradiotherapy neck dissection was planned for 21 of 26 patients (80%) as 17 (65%) had a PR and 4 (15%) had stable disease in the neck after induction chemotherapy (Table 3). This cohort included the 7 patients with primary site control and a neck PR after chemoradiotherapy (Table 4). Based on the planned treatment schema, 21 patients should have undergone a neck dissection; however, only 19 patients underwent neck dissection after chemoradiotherapy. Of these patients, 7 (32%) neck dissections were positive for residual disease. Forty-two percent (3 of 7) of the positive patients subsequently went on to develop recurrent disease. The remaining 58% of patients are alive with no evidence of disease (NED). Of 12 patients with pathologically negative neck dissections, only 3 developed recurrent disease (25%). The pattern of failure is shown in Table 5 and was evenly distributed between distant and local-regional failure.

Eleven patients did not undergo a neck dissection: 4 presented without nodal disease, 5 had a CR to induction chemotherapy and thus were not recommended to undergo surgery. Two who were planned for neck dissections did not undergo surgery: 1 patient had inoperable disease and 1 had progressive disease. Thus, of the 21 patients identified to

have a neck dissection based on the protocol algorithm, only 2 did not undergo the procedure for clinically appropriate reasons. Therefore, the overall treatment program—induction chemotherapy, chemoradiotherapy, and neck dissection, where indicated—rendered 28 of 30 (93%) patients with advanced SCCHN disease-free at the end of all therapy.

At present, a total of 8 of the 30 patients enrolled in the trial have died, including one who was clinically NED. Three patients had local-regional recurrences at 7, 13, and 43 months; the first died at 16 months and the second underwent salvage surgery and is alive NED at 28 months. The last patient developed a recurrence at 43 months near the primary site and could be considered a second primary or local recurrence. He died at 47 months. Four patients recurred both locally and distantly between 5 and 12 months, and all died between 6 and 14 months. One patient had distant disease only vs. a second primary at 22 months and died of disease at 26 months. It is notable that among the 5 patients who received carboplatinum/5-FU as their induction chemotherapy, 4 recurred (80%). By comparison, among the 25 patients who received a cisplatin-based regimen, a total of 4 have recurred (16%). One patient who was clinically NED died of anoxic brain damage, described below in “Toxicity.” Thus, among 30 patients, there were 7 deaths from cancer, 1 salvage surgery (alive and NED), and 1 toxic death. A total of 21 of 30 patients (70%) are currently alive and persistently NED. A Kaplan-Meier estimate of overall survival is 70% (Fig. 1). If we were to examine only those patients who had a “poor prognosis” based on their response to induction chemotherapy, there are 15 of 24 patients (63%) currently alive and persistently NED.

Radiation delivery

All patients completed their planned radiation therapy courses. Total doses delivered ranged from 6,900 to 7,230

Table 4. Response after docetaxel-radiation therapy: fractional response (percentage)

	CR	PR	SD	PD	RR
Primary site	23/26 (88.5)	1/26 (3.9)	1/26 (3.9)	1/26 (3.9)	24/26 (92.3)
Lymph nodes	18/26 (69.2)	7/26 (26.9)	1/26 (3.9)	—	25/26 (96.2)
Overall	21/30 (70.0)	7/30 (23.3)	1/30 (3.3)	1/30 (3.3)	28/30 (93.3)

Abbreviations as in Table 3.

Response for all patients after docetaxel/radiation therapy treatment, including the entire treatment course. Results are reported separately for primary and nodal sites.

Table 5. Recurrences/patient deaths

Site of recurrence	Initial stage/IC regimen used	Recurrence	Time of death
Lung/local*	T4N0 OPX/PF	4.6	6.3
Liver, lung, base of skull*	T3N3 Larynx/CF	11.8	12.3
Local (base of tongue)*	T4N2b OPX/CF	6.5	15.8
Bilateral lung	T4N2c Larynx/CF	21.9	26.4
Local, lung	T2N3 OPX/TPF	12.2	14.3
Local, lung*	T4N2b OPX/PF	4.7	9.1
Local*†	T2N3 OPX/TPF	13.4	NED
Local	T4N2c OPX/PF	42.7	47.4
Fibrosis/anoxic death	T4N2 OPX/PF	cNED	13.6
Summary of failures	Local recurrences	3	
	Distant metastases	1	
	LR + DM	4	

Abbreviations: OPX = oropharynx; AWD = alive with disease; cNED = clinically no evidence of disease; IC = induction chemotherapy; PF = cisplatin/5-fluorouracil; CF = carboplatin/5-fluorouracil; TPF = docetaxel-PF; LR = local recurrences; DM = distant metastases.

Tabulation of patients experiencing recurrences and/or death.

* Patient with positive neck dissection or patient with progressive disease/unresectable disease in neck.

† Recurrence treated with surgery and chemoradiotherapy. Alive with no evidence of disease at 28.7 months.

cGy, with a median of 7,230 cGy. Treatment time ranged from 39 to 57 days, with a median of 43 days. Three of 30 patients required greater than 45 days and only 1 over 50 days to receive the planned course of radiation.

Toxicity

There was no acute dose-limiting toxicity observed in any patient treated at either dose level. After treatment of the first 3 patients at 20 mg/M², the initial plan had been to treat all subsequent patients at the higher, 25 mg/M², dose level. This was accomplished without any acute dose-limiting toxicity being seen. However, with longer follow-up there were concerns regarding the duration of PEG dependence, indicating a potential late toxicity. Rather than continuing with the original dose escalation plan, a decision was made to enroll additional patients at the lower, 20 mg/M², dose level. Table 6 compares the two groups in terms of PEG dependence and demonstrates

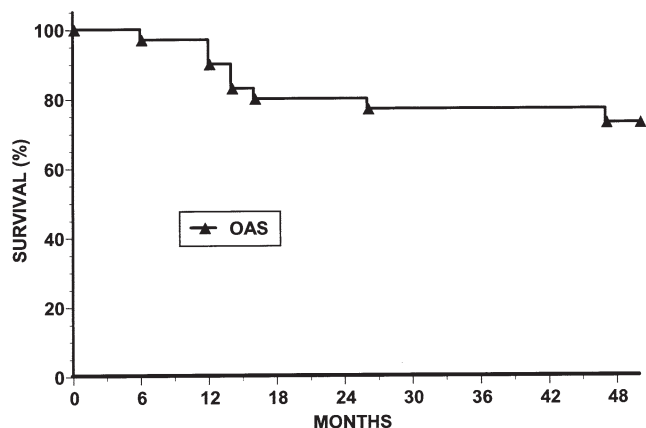


Fig. 1. Overall survival (OAS). Kaplan-Meier survival curve for the 30 patients treated on the docetaxel concomitant boost protocol.

a decreased duration of dependence for the patients treated at the lower dose level. The median duration of PEG dependence for the patients treated at 20 mg/M² was 6.3 months with a range of 3.9 to 16.3 months; 1 patient has a PEG remaining at 26 months. This is to be compared with the median of 10.3 months and range of 2.7 to 21.2 months for the patients treated at a dose of 25 mg/M². Of note, the patient who had his PEG removed at 2.7 months only received his cone-down boost to the ipsilateral neck, as he had presented with an unknown primary.

All patients developed Grade 3 or 4 mucositis (National Cancer Institute Clinical Trials Implementation Committee version 2) during chemoradiotherapy, as expected with an aggressive radiation and chemotherapy regimen. With respect to long-term toxicity, 20% of the entire population required esophageal dilations to continue swallowing. Tracheotomies after radiotherapy were required in 2 of the 15 patients treated at the higher dose level, and 1 patient in this group died of late fibrosis. He had presented with a T4N2 oropharyngeal lesion, required a tracheostomy before chemoradiotherapy, and had a negative postchemoradiotherapy biopsy. After recovering from acute toxicity, his tracheostomy was decannulated. Fourteen months after radiation, the patient experienced a fatal respiratory emergency and anoxic brain injury but was apparently disease-free.

Overall, 37% of all patients developed hypothyroidism, comparable in the two groups. It is likely that some background level of increased toxicity was contributed by the prior induction chemotherapy treatment, although patients treated at both dose levels received prior therapy.

DISCUSSION

In the present study, we report Phase I/II data from a concomitant boost radiation schedule given with 4 weekly

Table 6. Toxicity data

	20 mg/M ²	25 mg/M ²	Total
Duration of PEG dependence			
Median (months)	6.9	10.3	7.6
Range (months)	3.9–22.4	2.7–21.2	2.7–22.4
Tube in place (<i>n</i> =)	1	—	1
Late toxicities			
Required dilatation	4/15	2/15	6/30
Tracheotomy after radiation	0/15	2/15	2/30
Hypothyroidism	6/15 (6.8–18 months)	5/15 (3.7–21.9 months)	11/30

Abbreviation: PEG = percutaneous endoscopic gastrostomy.

concurrent doses of docetaxel in the context of prior platinum-based induction chemotherapy. We have used the docetaxel/radiation combination in the postinduction setting as part of a sequential treatment model for patients with advanced SCCHN and, in most cases, exceptionally poor prognosis. The focus of this discussion will be the investigational component of our protocol, the local-regional chemoradiotherapy treatment regimen.

The optimal treatment for local-regional management of locally advanced head-and-neck cancer remains controversial. Research into identifying the most appropriate combination of therapies has focused on modifications of the radiation schedule or adding systemic therapy to once a day radiation. A number of “altered fractionation” radiation regimens have been used to improve responses compared with SF radiation, based on multiple radiobiologic rationales (1, 2, 28). The recent, definitive, Phase III study (RTOG 90-03) demonstrated that both AF/CB and hyperfractionation yielded the best local and regional disease control (5). The concomitant boost schedule is based on addressing the accelerated tumor repopulation, which is seen later in a course of therapy, by increasing the daily radiation dose at this point in the treatment program. The other approach to improving local-regional control in SCCHN builds on a framework of SF radiation by adding concurrent chemotherapy, primarily as a radiation sensitizer. Based on our prior study of docetaxel and chemotherapy with SF and the RTOG data, we hypothesized that the AF/CB regimen combined with docetaxel might be advantageous for local control and toxicity (5, 18). Thus, we integrated our prior docetaxel/chemoradiotherapy with the concomitant boost radiation schedule in this Phase I/II study.

Emerging data from single-agent studies in advanced and/or metastatic disease have prompted the inclusion of the taxanes into multiagent and multimodality treatment of head-and-neck cancers (27, 29–31). Only a limited number of studies have used single-agent docetaxel concurrently with radiation, and none of these with an altered fractionation schedule. An initial Phase I study of docetaxel with daily radiation for SCCHN did not progress beyond the first dose level of 15 mg/M² (32). The severe toxicities observed in this study, including Grade 4 skin, pulmonary reactions, and Grade 3 thrombocytopenia were not seen in subsequent Phase I/II studies, most of

which used higher weekly doses of docetaxel. The reason for the broader and more toxic reactions seen in this initial trial is not clear. We performed a Phase I study of docetaxel with concurrent standard fractionated radiotherapy and established an maxillary tolerated dose (MTD) of 25 mg/M² for a group of poor prognosis patients following induction chemotherapy (18). Excellent clinical responses and survival were observed, although local and regional toxicity were increased. Two additional Phase I studies, both of which started at 10 mg/M², found lower MTDs than our study, with mucositis being the dose-limiting toxicity. In one trial, 15 mg/M² was found as the MTD (33), whereas the other did not progress beyond the initial dose of 10 mg/M² (34). Among trials using other agents in combination with docetaxel, the M. D. Anderson Cancer Center has examined a concomitant boost radiation schedule similar to that investigated here (35). They also limited systemic treatment to four doses, consisting of docetaxel at 15 mg/M² and cisplatin at 20 mg/M², which they established as the combined MTD in a Phase I trial. Dose-limiting toxicities were prolonged mucositis and Grade 3 skin toxicity. The combined use of cisplatin with docetaxel and the possible interactions between the two agents may contribute to the lower final dose levels. The results of the follow-up Phase II study, only available in abstract form, appear quite promising.

The experience with a combination of altered fractionation radiation and concurrent chemotherapy is limited at present. The initial set of Phase III studies was designed around standard agents (cisplatin, carboplatin, and 5-FU). Brizel *et al.* (13) examined hyperfractionated radiation with and without chemotherapy (1.25 Gy twice a day to 70 Gy with cisplatin, 5-FU vs. 1.25 Gy twice a day to 75 Gy) and reported toxicity, both short-term and long-term, to be similar in the two arms. There were nonsignificant improvements in overall survival, relapse-free survival, and a statistically significant improvement in local-regional control (70% vs. 44%, *p* = 0.01) for the combined modality arm. A similar hyperfractionated regimen (1.1 Gy twice daily to 77 Gy [9, 10]) was used in combination with low-dose cisplatin (6 mg/M²) given daily between the two radiation fractions. There were statistically significant increases in 5-year overall sur-

vival (OAS), progression-free survival, local-regional progression-free survival, and distant metastases-free survival for the combined modality arm. The decrease in distant metastatic disease observed was surprising, given the modest daily dose of single-agent cisplatin and the unusual schedule used. Acute, nonhematologic toxicity was similar in the two groups, whereas hematologic toxicity was increased for the combined modality arm.

An unorthodox, split-course radiation schedule was used by Wendt *et al.* (36), which consisted of three courses of 1.8 Gy twice-daily radiation (total dose = 23.4 Gy); in the investigational arm it was interspersed with cisplatin, 5-FU, and leucovorin. This study showed an improvement in local control (17% vs. 36% at 3 years, $p < 0.004$) and OAS (24% vs. 48%, $p < 0.003$) though the absolute magnitude of both results in the control arm was somewhat disappointing. Unfortunately, the nonstandard split-course radiation-only control arm may be significantly inferior to continuous treatment plans, as was recognized by Brizel *et al.* (13) in their treatment design.

A more mixed, cautionary message on the advantage of the combination of altered fractionation with radiation comes from the rigorous and highly informative study of Staar *et al.* (37). Their radiation schedule was a slight variation of the standard AF/CB regimen; they used 1.8 Gy once-daily followed by 1.8 Gy/1.5 Gy twice a day to a total dose of 69.9 Gy. This radiation schedule was used with or without two cycles of 5-FU/carboplatin. This study included both hypopharynx and oropharynx patients. Comparable rates of responses (CR + PR) were seen for both the radiation and the chemoradiotherapy arms (92% vs. 88%). There was a significant benefit for the oropharynx patients treated with combined modality therapy, which was not seen for the hypopharynx population. This benefit in oropharyngeal patients was seen for survival with local-regional control, 60% compared with 40% ($p = 0.01$). The study is also noteworthy for the significant amount of toxicity that was reported by the investigators. Although there was the expected increase in acute toxicity for the combined modality arm, there was also a dramatic increase in swallowing problems among 2-year survivors and a continued requirement for a feeding tube. Swallowing problems were also seen in a large number of the radiation-alone patients (51% vs. 25%, $p = 0.01$). A similar result was obtained in a Phase II study of concomitant boost and bolus cisplatin, which reported a 27% rate of PEG dependence among 2-year survivors (38).

Another study employed concurrent radiotherapy with carboplatin-docetaxel, following an induction regimen using the same drugs; 15 of 20 patients treated with this induction chemotherapy responded and went on to receive chemoradiotherapy (39). The concurrent combination used up to 20 mg/M² docetaxel and carboplatin at area under curve 2 and was well tolerated. Overall response was good (13/15), reported with short follow-up.

Our data demonstrate that weekly docetaxel and con-

comitant boost radiation therapy is very active and compares quite favorably with efficacy and toxicity data in the literature. All of our patients received this therapy after induction chemotherapy. These results were obtained in a patient population where the majority of patients were known to have poor prognosis, based on their response to induction chemotherapy. Laboratory studies have shown that taxane added to radiation can be effective even in chemotherapy-resistant (even including taxanes) disease; our clinical data give further support to that finding. The data of Staar *et al.* (37) and Ang *et al.* (38) indicate the level of toxicity that can result from AF/CB radiation alone or as part of an aggressive combined regimen, and our data compare quite favorably with theirs. Our patients had a lower rate of PEG dependency, which may arise from a number of factors, such as patient selection, postinduction improvements in physiology and structure of the swallowing tissues (such that dysphagia is improving before the start of chemoradiotherapy), early recognition of the problem and intervention, an integrated management plan to dilate patients early after healing, and the initiation of swallowing therapy early in the course of recovery (40). Based on our findings, this combination offers an active and aggressive treatment strategy for high-risk patients in a sequential therapy model where the response to induction chemotherapy is known before beginning local-regional therapy. Additionally, the combination of docetaxel and AF/CB can be considered as a potential initial treatment for selected advanced SCCHN. In the postinduction setting, the optimal dose is likely 20 mg/M². Our data indicate that we were able to consistently deliver this planned treatment, giving the prescribed radiation dose, with only 1 of 30 patients requiring more than an extra few days to complete the planned treatment course.

As we move forward with combinations of systemic therapy and altered fractionation schedules, it is clear that the "price" patients pay for increased tumor control is the increased toxicity resulting from the combination of the two modalities. Along with the push for optimal therapeutic combinations, there is an added reason to integrate techniques that minimize toxicity. Within the radiation realm, this means an increased use of techniques, such as intensity-modulated radiation therapy, that have a track record of being able to decrease xerostomia. This technique is now used more frequently, but has limitations with respect to normal tissue sparing when treating advanced disease. Approaching the problem from the pharmacologic viewpoint, many newer agents, including drugs such as amifostine, targeted agents such as epidermal growth factor receptor inhibitors, and growth factors can help to limit or control local toxicity. These agents can modulate the side effects of these more effective yet toxic chemoradiotherapy combinations and offer systemic efficacy with less side effects. Future trials will address the optimal methods for integrating them into treatment programs.

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