

# Multicenter Phase I-II Trial of Docetaxel, Cisplatin, and Fluorouracil Induction Chemotherapy for Patients With Locally Advanced Squamous Cell Cancer of the Head and Neck

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**Purpose:** We conducted a phase I-II, multi-institutional trial to determine the maximum-tolerated dose (MTD) of cisplatin in an induction chemotherapy regimen of docetaxel, cisplatin, and fluorouracil for squamous cell cancer of the head and neck (SCCHN) and to determine the safety, tolerability, and efficacy of the regimen at MTD.

**Patients and Methods:** A total of 43 patients with previously untreated, locally advanced, curable SCCHN were entered. Overall, 29 patients (67%) had N2 or N3 nodal disease and nine (21%) had T4 primary tumors. All patients received docetaxel 75 mg/m<sup>2</sup> on day 1; cisplatin at 75 (level I) or 100 (level II) mg/m<sup>2</sup> on day 1; and a continuous fluorouracil infusion at 1,000 mg/m<sup>2</sup>/d on days 1 through 4. Patients were treated with prophylactic antibiotics on days 5 through 15. Cycles were repeated every 21 days for a total of three cycles. Patients then received definitive therapy based on institutional preferences.

**Results:** Thirteen patients were treated at level I, and 30 patients were treated at level II. All 43 patients were assessable for toxicity. There were no major differences in toxicity between level I and level II. Cisplatin-associated grade 3 or 4 hypomagnesemia or hypocalcemia

occurred in 13 (30%) and hearing loss in two patients (5%). Grade 3 or 4 neutropenia was observed in 41 patients (95%) and febrile neutropenia occurred in eight (19%). There was one serious infection (2%). There were 17 (40% [95% confidence interval [CI], 25% to 56%]) clinical complete responders (CR), 23 (54% [95% CI, 39% to 69%]) partial responders (PR), one (2%) with no change, and two (5%) unassessable patients. Major responses (CR, PR) were observed in 40 (93% [95% CI, 81% to 99%]) patients. Primary site CR was documented in 24 (54%) of patients. Postchemotherapy primary site biopsies were performed in 25 patients (58%) and pathologically negative biopsy was obtained in 11 (92%) of 12 primary site clinical CRs and seven (54%) of 13 with PR or no change. Overall, negative biopsies were obtained in 18 patients (72%).

**Conclusion:** TPF induction chemotherapy can be delivered safely with a cisplatin dose of 100 mg/m<sup>2</sup> in previously untreated patients with SCCHN. The regimen is associated with a high rate of primary site clinical and pathologic CRs. Phase III comparison with cisplatin and fluorouracil chemotherapy is warranted.

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COMBINATION CHEMOTHERAPY with cisplatin and fluorouracil (PF) is the standard treatment for patients with locally advanced squamous cancer of the head and neck (SCCHN) receiving induction chemotherapy.<sup>1,2</sup> As originally described, PF chemotherapy is an effective replacement for surgery in patients with larynx, hypophar-

ynx, and oropharyngeal tumors.<sup>3,4</sup> PF chemotherapy has also been shown to increase survival and disease-free survival in patients with unresectable disease when given before definitive radiotherapy.<sup>5</sup> In randomized trials, the response rates for treatment-naïve patients with locally advanced disease varies between 75% and 85%. Complete responses (CR) are seen in only 25% to 35% and primary site CR rates are between 35% and 55%.<sup>3-5</sup> CR rates and primary site pathologic CR rates have been shown to predict local-regional control.<sup>6-9</sup> Randomized trials for organ preservation have recruited limited numbers of patients with advanced (N2 and N3) nodal disease and fewer CRs occur in these patients.<sup>3,4</sup> Despite the high overall response rates, the low CR rates at the primary site and in patients with extensive nodal disease are disappointing and are associated with poor survival in advanced-stage disease.

These results have stimulated intensive investigations of new agents and combinations in an attempt to improve on complete clinical responses and on primary site pathologic response rates. The addition of leucovorin to PF (PFL)

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resulted in high CR rates at the cost of significant toxicity.<sup>10-12</sup> Carboplatin has proven to be less effective than cisplatin in randomized trials, and the addition of interferon alfa to PFL has not improved responses while increasing toxicity.<sup>13-15</sup> The taxanes have demonstrated considerable single-agent activity in recurrent SCCHN. In recurrent, incurable patients, response rates at the maximum-tolerated dose (MTD) have varied between 25% and 42% for taxane monotherapy.<sup>16-19</sup> Taxanes exert their anticancer effects by mechanisms of action that differ from those of cisplatin and fluorouracil (5-FU). The major toxicity of the taxane docetaxel is highly predictable myelotoxicity. Neuropathy, a dominant side effect of cisplatin, is minimal with docetaxel, although there is a small incidence of mucositis with this agent. The differences in mechanisms of action and relatively nonoverlapping toxicities of taxanes compared with PF have prompted investigators to examine the potential of adding docetaxel to PF and PF-related combination therapy. At least two studies in previously untreated patients with locally advanced SCCHN have explored the use of docetaxel incorporated into a highly aggressive PFL-based chemotherapy.<sup>20,21</sup> Both studies demonstrated high primary site CR rates and overall CR rates. Toxicity with these regimens was considerable, and the patient populations were highly selected. Comparison of the results with the original PFL studies demonstrates enhanced responses and suggests that docetaxel added to the efficacy of the basic PFL regimen.

We performed the present phase I-II study to establish an MTD for cisplatin in a treatment combination, TPF, that incorporates docetaxel into PF chemotherapy. Because of the potential added toxicity of docetaxel and cisplatin, we decided to test whether the standard cisplatin dose of 100 mg/m<sup>2</sup> or a lower dose would be safe and tolerable. Thus, in the phase I segment of this study, we evaluated 75 and 100 mg/m<sup>2</sup> of cisplatin in a TPF combination regimen that added docetaxel at a dose of 75 mg/m<sup>2</sup> to PF. 5-FU was reduced by 20%, or 1 day, from the PF standard because of the moderate risk of increased mucositis, and antibiotic prophylaxis was added for the increased risk of neutropenia. In the phase II segment of this study, we established the efficacy and safety profile of TPF at the established dose.

## PATIENTS AND METHODS

### *Patient Population*

This study was approved by the Human Protection Committee at each of the participating institutions. It was required that patients give informed consent before entry onto this study. Patients were eligible if they had histologically or cytologically confirmed SCCHN, at least one unidimensionally measurable lesion, and stage III or IV disease without evidence of distant metastases. Patients with primary sites in the larynx,

hypopharynx, oropharynx, or oral cavity were eligible. Patients with unknown primary cancers, nasopharynx cancer, salivary gland cancer, and cancers arising in the paranasal sinuses were specifically excluded from the study. Patients who had received previous chemotherapy were specifically excluded, and patients who had been treated with definitive surgery or any radiotherapy for a previous SCCHN were excluded. Patients were ineligible if they had another cancer, other than basal or squamous cancer of the skin or carcinoma-in-situ of the uterine cervix, within 5 years of study entry.

Patients were required to be 18 years of age or older and have an Eastern Cooperative Oncology Group performance status of 1 or better. Patients were required to have adequate nutritional intake and were excluded if they required intravenous (IV) alimentation to maintain adequate nutrition. Patients were excluded if they had a serious concomitant illness or medical condition, including chronic obstructive pulmonary disease requiring hospitalization within the last year; myocardial infarction within 6 months; symptomatic angina pectoris; arrhythmias other than stable atrial fibrillation; uncontrolled hypertension; active infection; active neurologic or psychiatric disorder; concurrent treatment with corticosteroids, unless chronic, for greater than 1 month and at low dose, equivalent to less than 20 mg/d of methylprednisolone; active peptic ulcer disease; uncontrolled diabetes mellitus; or pregnancy.

For study entry, patients were required to have adequate bone marrow, hepatic, and renal function assessed within 7 days of entry. An absolute neutrophil count and platelet count of  $\geq 2 \times 10^9/L$  and  $100 \times 10^9/L$ , respectively, were required. A normal bilirubin and limited elevations of AST or ALT to  $\leq 1.5$  times the upper limit of normal (ULN) and alkaline phosphatase  $\leq$  five times the ULN were allowed. A calculated or actual creatinine clearance more than 60 mL/min was required for study entry. Patients were also required to have a normal serum calcium.

Required prestudy testing for entry included a complete history and physical examination with baseline evaluation of toxicity and symptoms; complete blood cell count (CBC) with differential and platelet count; hepatic function testing; blood urea nitrogen, electrolytes and creatinine; serum calcium, magnesium, total protein, albumin, glucose, and uric acid; urine analysis; 12-lead ECG; posteroanterior and lateral chest x-ray; computed tomography or magnetic resonance imaging of the sites of disease; serum or urine human chorionic gonadotropin for women of child bearing potential. A tumor-node-metastasis staging assessment based on physical examination and radiologic studies was performed within 4 weeks of study entry.<sup>22</sup> When performed, an examination under anesthesia was used to support staging determinations.

### *Treatment*

It was expected that patients would be treated in the outpatient setting and that patients would receive three cycles of chemotherapy, delivered at 3-week intervals. Patients were required to receive dexamethasone 8 mg PO bid beginning the night before therapy for a total of six doses and ciprofloxacin 500 mg PO bid or equivalent for 10 days beginning on day 5 of treatment. Immediately before treatment, all patients received antiemetic therapy with a 5-HT<sub>3</sub> antagonist which was continued on an appropriate schedule according to institutional practice. On day 1, all patients received docetaxel 75 mg/m<sup>2</sup> as a 1-hour infusion, followed by hydration with 750 to 1,000 mL of 0.9% sodium chloride. Patients were then treated with mannitol 12.5 g as an IV bolus, followed by cisplatin, 75 or 100 mg/m<sup>2</sup> in a minimum of 250 mL 0.9% sodium chloride for 0.5 to 1.0 hour. Postcisplatin hydration consisted of 1,000 mL of D5/0.45% sodium chloride solution with 25 g

of mannitol for 4 hours and 20 Meq KCl given IV or orally. A continuous 5-FU infusion was begun immediately after completion of the cisplatin infusion at 1,000 mg/m<sup>2</sup>/d for 4 days, for a total planned dose of 4,000 mg/m<sup>2</sup>/cycle. The 5-FU infusion was completed on day 5. It was required that patients be monitored during the first 24 hours of each cycle for adequate oral fluid intake, and it was highly recommended that patients return on day 2 for additional IV hydration and antiemetics. Patients were urged to wash their mouths with saline rinses eight times per day during and immediately after therapy during the period of mucositis. Treatments were repeated every 3 weeks.

During treatment, patients were evaluated with a weekly CBC, differential, and platelet count. Patients with fever were evaluated, and those with febrile neutropenia were required to have a CBC and differential at least every 2 days until recovery to an ANC more than  $0.5 \times 10^9/L$  and resolution of fever ( $< 38.1^\circ C$ ). Before the initiation of the second and third cycles, patients were to have a physical examination, history, toxicity evaluation, CBC with differential and platelet count; hepatic function testing; blood urea nitrogen, electrolytes and creatinine; serum calcium, magnesium, total protein, albumin, glucose, and uric acid.

### *Toxicity Assessment and Dose Modifications*

Toxicity was evaluated according to the 1995 edition of the National Cancer Institute common toxicity criteria. Before initiation of the second or third cycle, mucositis, diarrhea, and myelosuppression should have resolved. Failure to resolve these toxicities for more than 2 weeks after completion of the cycle would result in the patient's being taken off the study. Patients with febrile neutropenia or a delay in therapy as a result of myelosuppression were to be treated with granulocyte colony-stimulating factor (G-CSF) on subsequent cycles.

Doses of each drug were modified according to the toxicity encountered. For myelosuppression, not controlled with G-CSF, docetaxel was to be reduced from 75 mg/m<sup>2</sup> to 60 mg/m<sup>2</sup>. Patients with hepatic function abnormalities developing during therapy had dose reductions of docetaxel to 60 mg/m<sup>2</sup> if there were an increase in AST or ALT to between 2.5 and five times the ULN with the alkaline phosphatase  $\leq$  2.5 times the ULN or if the alkaline phosphatase were between 2.5 and five times the ULN and the AST or ALT were between 1.5 and five times the ULN. Elevations of any of these enzymes to more than 5 times the ULN called for holding the docetaxel for a maximum of 2 weeks and taking the patient off study if recovery did not occur in that time frame. For grade 4 thrombocytopenia, cisplatin was to be reduced from 100 mg/m<sup>2</sup> to 75 mg/m<sup>2</sup> with a further 20% reduction if grade 4 thrombocytopenia recurred. Patients with grade 3 neurotoxicity were discontinued from study, and patients with a grade 2 neurotoxic event were re-treated with a 20% reduction in cisplatin dose on recovery to grade 1 or better. Patients with diarrhea were treated with loperamide; however, for patients with grade 3 diarrhea for more than 7 days or grade 4 diarrhea despite loperamide, a 10% reduction in the daily dose of 5-FU was required. If grade 3 or 4 diarrhea recurred on a subsequent cycle, then the 5-FU dose was to be further reduced to 800 mg/m<sup>2</sup>/d. For mucositis grade 3 lasting more than 5 days or grade 4 mucositis, the daily 5-FU dose was reduced 20%. Patients with a grade 4 mucositis despite dose reduction were discontinued from the study. For grade 4 skin toxicity, treatment was delayed until resolution to grade 1 or less, and the 5-FU dose was reduced by 20% on the subsequent cycle.

The MTD of cisplatin was to be determined in this combination as either 75 mg/m<sup>2</sup> or 100 mg/m<sup>2</sup> dose levels I and II, respectively. Dose-limiting toxicity (DLT) was defined for this study. Although any of the following DLTs would define DLT for an individual patient, for a DLT to be used to define the cisplatin dose level as unacceptable, the

same DLT had to be observed in at least three of six patients at that dose level. DLT myelotoxicity was grade 4 neutropenia more than 7 days despite G-CSF; grade 3 or 4 neutropenia with grade 2 fever lasting more than 3 days; or a platelet count of less than  $25 \times 10^9/L$ . Other DLTs were defined as grade 3 or 4 infection; grade 3 or 4 elevation of bilirubin, AST, ALT, or alkaline phosphatase; grade 4 vomiting, grade 3 or 4 diarrhea with prophylactic treatment; grade 3 dermatitis; and grade 3 sensory or motor neuropathy.

Dosage escalation between the two dose levels was strictly controlled for patient safety. At least two patients were to be treated at level I and observed for 4 weeks before a third could be added. The third patient had to be observed for a minimum of 2 weeks before dose escalation to level II. If no DLTs were observed, two patients were to be treated at level II and observed for 2 weeks before a third could start. The third patient needed to be observed for an additional 2 weeks. During the waiting periods, additional patients could be accrued to level I. If one or two of three patients developed a DLT at level I, an additional three patients would be added. If two of six patients developed a DLT at dose level I, further escalation would be halted and dose level I declared the MTD. If three of six patients developed DLT, then the cisplatin dose was to be de-escalated to 60 mg/m<sup>2</sup>. At level II, if no DLT were observed in the first three patients, level II would be selected as MTD. If two of three patients developed a DLT, then level I would be selected as MTD. If one of three patients developed a DLT, then an additional three patients would be added. If two of six patients developed a DLT at dose level II, dose level II would be selected for further study. If three of six patients developed DLT, then level I would be selected for further study.

### *Response Assessment*

Patients were assessed for clinical response before the start of cycle 3 and then again between days 14 and 35 of cycle 3. Investigators were urged to assess pathologic response by performing an examination under anesthesia and multiple surgical biopsies of the primary site in patients between days 14 and 35 of cycle 3; however, this was not required. To assess response, patients were required to have an adequate baseline assessment within 4 weeks of the start of treatment. Patients were considered assessable for response if they received a minimum of two cycles of treatment with at least one follow-up assessment that was assessable for response. The same technique used for baseline measurement was required for final response assessment. Either clinical or radiographic assessment was permitted, and two observers were required to review response assessment. Complete clinical response was defined as the disappearance of all known disease. A pathologic complete primary site response was defined as no evidence of tumor in the repeat primary site biopsy. A partial response (PR) for bidimensionally measurable disease was defined as at least a 50% decrease in the sum of the products of the largest perpendicular diameters of all measurable lesions. A PR for unidimensionally measurable disease was defined as at least a 50% decrease in the sum of the largest diameters of all measurable lesions. For a PR, it was not necessary for all lesions to regress, but there could be no progression and no new lesions. No change was defined as less than 50% decrease or a 25% increase in the sum of the products of the largest perpendicular diameters of all measurable lesions. For unidimensionally measurable disease, no change was defined as less than a 50% decrease or a 25% increase in the sum of the largest diameters of all measurable lesions. Progressive disease was defined as more than a 25% increase in the sum of the products of the largest perpendicular diameters of all measurable lesions or sum of the largest diameters of all measurable lesion or the appearance of any new lesions. Responses in the primary

**Table 1. Patient Characteristics**

	Level I Cisplatin 75 mg/m <sup>2</sup>	Level II Cisplatin 100 mg/m <sup>2</sup>	All
Patients	13	30	43
Assessable for response	12	29	41
Sex, male:female	10:3	22:8	32:11
Age, years			
Median	54	58	57
Range	26-75	28-70	26-75
Primary tumor site	13	30	43
Oropharynx	7	15	22
Hypopharynx	2	6	8
Larynx	2	5	7
Oral cavity	2	4	6
Performance status			
ECOG 0	7	21	28
ECOG 1	6	9	15

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

site and the regional nodes were scored separately and the overall response based on the worst of the two responses.

The phase I portion of the trial was planned to accrue a minimum of six and a maximum of 12 patients. Based on these plans, there was a 91% probability of escalating if the true DLT rate were 10%, and a 17% probability if the true DLT rate were 50%. If the true DLT rate at level II were 50%, then the probability of selecting level I was 69%. The overall accrual for phase II was 29 patients assessable for tumor response at MTD. The null hypothesis that the true CR rate was less than 20% was tested against an alternative rate of 45%. With 29 patients, the null was to be rejected if 10 patients (34.5%) achieved a clinical CR.

## RESULTS

### Patients

A total of 43 patients were entered on this trial between February and December 1998. Thirteen patients were entered on level I and 30 patients on level II. The characteristics of the population are listed in Table 1 and the tumor-node-metastasis staging is listed in Table 2. As can be seen from Table 1, this was a well-distributed population of patients with an excellent performance status. The largest group of patients had oropharyngeal lesions, which included a preponderance of base-of-tongue primary tumors in which preservation of tongue function would be important. Larynx and hypopharynx tumors, for which organ preservation is also a significant concern, were also well represented.

The tumor-node-metastasis staging of all patients entered is listed in Table 2. There was one patient with stage III and 12 patients with stage IV tumors treated at level I, and 10 patients with stage III and 20 patients with stage IV tumors treated on level II. N2 and N3 nodal disease were present in 11 patients (85%) in level I and 17 patients (57%) on level II. Overall, 28 patients (65%) had N2 or N3 nodal disease

**Table 2. TNM Staging**

	T1	T2	T3	T4	
Level I-Cisplatin 75 mg/m <sup>2</sup>					
N0	—	—	—	1	1
N1	—	—	1	—	1
N2	1	2	5	1	9
N3	—	—	1	1	2
	1	2	7	3	13
Level II-Cisplatin 100 mg/m <sup>2</sup>					
N0	—	—	6	2	8
N1	—	1	3	1	5
N2	1	2	7	3	13
N3	1	2	1	—	4
	2	5	17	6	30

before the start of induction chemotherapy. T4 primary tumors were present in three patients (23%) and six patients (20%) treated on level I and II, respectively.

Although prophylactic antibiotics were mandated as part of treatment planning, only 12 of 13 patients at level I received antibiotic treatment per protocol. Among level II patients, 23 received antibiotics on cycle 1 and 20 of 29 on cycles 2 and 3. Thus 30% of the patients treated on level II did not receive prophylactic antibiotics because of protocol violations.

All patients were assessable for toxicity; two patients were unassessable for response. One patient treated at level I received all three cycles of chemotherapy but did not have an appropriate radiologic restaging after chemotherapy. A patient treated at level II received only one cycle, complicated by hypocalcemia and hypomagnesemia. This latter patient underwent a previous, remote renal transplantation and had underlying acquired hypoparathyroidism, which contributed to this toxicity.

### Toxicity

Grade 3 and 4 toxicity at both dose levels was modest and is presented in Table 3. No DLT was encountered in the first three patients entered at level I and escalation to level II proceeded. At level II, there was no DLT in the first six patients and full accrual completed to 30 patients at level II. Additional patients were entered at level I during the required observation periods during the phase I testing period of patient entry to level II. All 43 patients were assessable for toxicity. All 39 possible cycles were administered at level I and 87 of 90 possible cycles were administered at level II. As mentioned, one patient at level II stopped study treatment after one cycle because of hypocalcemia and hypomagnesemia, and another patient completed two cycles, developed grade 3 limiting neuro-hearing loss, and did not complete a third cycle on protocol.

**Table 3. Per Patient Incidence of Grade 3 and 4 Toxicity**

Dose Level Toxicity*	Level I	Level II	Total	
	Cisplatinum 75 mg/m <sup>2</sup>	Cisplatinum 100 mg/m <sup>2</sup>	No. of Patients	%
Assessable patients	13	30	43	
Stomatitis	6	7	13	30
Diarrhea	2	2	4	9
Renal-metabolic	3	10	13	30
Dehydration	0	3	3	7
Vomiting	1	2	3	7
Nausea	2	6	8	19
Allergy	1	0	1	2
Neutropenia	13	28	41	95
Febrile neutropenia	2	6	8	19
Infection	0	1	1	2
Thrombocytopenia	1	1	2	5
Neuro-hearing	1	1	2	5
Liver enzyme	0	2	2	5
Fatigue	1	0	1	2

\*No grade 3 or 4 toxicity occurred for sensory or muscular neuropathy or skin.

Dose reductions occurred in seven patients treated at each dose of cisplatin. At level I, two patients had cisplatin modified for reduced creatinine clearances, three patients had 5-FU reduced for stomatitis, and one patient had docetaxel reduced for grade 3 fatigue. At level II, five patients had 5-FU reduced for stomatitis, and one had docetaxel reduced for liver enzyme elevation. One patient at each dose level had a reduced dose of 5-FU on a single cycle as a result of incorrect dose calculations.

Severe stomatitis occurred in 30% of all patients and was unrelated to cisplatin dose. Severe diarrhea was rare and was likewise unrelated to cisplatin dose. There were no significant reductions in creatinine clearance; however, hypomagnesemia and hypocalcemia occurred in 30% of patients. Three patients at level I and seven at level II had grade 3 hypomagnesemia. Two patients at level II had grade 4 hypocalcemia and one had grade 4 hypomagnesemia. One patient described above had a significant confounding hypoparathyroidism and contributed two of the incidents of grade 4 abnormalities (hypomagnesemia and hypocalcemia) at level II. Likewise, nausea and vomiting were unaffected by cisplatin dose, although severe dehydration developed in 10% of the patients at level II and no patients at level I, suggesting a cumulative increase in cisplatin-related effects. Neuro-hearing loss occurred in one patient at each cisplatin dose, and no neuro-sensory or neuro-muscular grade 3 or 4 toxicities were encountered. Liver enzyme abnormalities were rare; however, two patients had grade 3 liver function abnormalities. One patient had an ALT elevation, and one had a bilirubin elevation; all episodes resolved.

The addition of docetaxel led to hematologic toxicity, principally neutropenia. Thrombocytopenia was rare; grade 3 occurred in one patient at each dose level. Ninety-five percent of the patients experienced grade 3 or 4 neutropenia. The median nadir was  $0.4 \times 10^3/\text{mm}^3$ , occurred on day 11, and recovered to normal in 7 days in both cisplatin dose levels. Three patients on level I and 10 patients on level II experienced grade 4 neutropenia for more than 7 days. Febrile neutropenia occurred in two patients on level I and six patients on level II. There were 11 episodes of febrile neutropenia among these eight patients. Only three episodes lasted more than 3 days. Six occurred on cycle 1, one on cycle 2, and four on cycle 3. Patients fully recovered in all 11 episodes, and no patient stopped or was removed from treatment for an episode. Cases of febrile neutropenia were associated with stomatitis (seven episodes) and diarrhea (six episodes). Although five patients developed documented infections during protocol treatment, only one case was serious and occurred during neutropenia on level II.

### Responses

Of the 43 patients entered, 41 were assessable for response. Two patients, one at each dose level, were not assessable, but are included in an intent-to-treat analysis. The single unassessable patient at level I had a different imaging method used to assess tumor response after completing all therapy, and the patient at level II went off study for toxicity after one cycle. As can be seen in Table 4, there were six complete clinical responses (46%) at level I and 11 (37%) at level II. Thus the overall complete clinical response rate was 40% (95% confidence interval [CI], 25% to 56%). In addition to CRs, there were five (39%) and 18 patients (60%) who had PR in level I and level II, respectively, for an overall PR rate of 54%. There was one patient with stable disease at level I. Thus 40 patients, or 93% (95% CI, 81% to 99%), had major responses.

Responses at the primary site were analyzed separately. As can be seen in Table 5, eight (62%) patients at level I and 16 patients (53%) at level II had primary site CRs, for an overall primary site CR rate of 56% (95% CI, 41% to 71%). As listed in Table 6, primary sites in 25 (58%) of 43 patients were biopsied. The remaining patients were not biopsied because of physician preference. Among the 25 biopsies, 13 of 17 or 76% of primary site PRs were biopsied and 12 of 24 or 50% of primary site CRs were biopsied. Eighteen (72%) of 25 biopsies were negative. Importantly, 54% of the biopsied patients with primary site PRs had a negative biopsy, whereas 8% of CRs had an unexpected positive biopsy. One patient assessed as no change (level I) overall had a PR at the primary site and a negative biopsy.

**Table 4. Clinical Responses**

Response	Level I (n = 13)		Level II (n = 30)		Overall (n = 43)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
CR	6	46	11	37	17	40
95% CI						25-56
PR	5	39	18	60	23	54
95% CI						39-69
NC	1	8	0		1	2
NA	1	8	1	3	2	5
CR + PR	11	85	29	97	40	93
95% CI		55-98		83-100		81-99

Abbreviations: NC, no change; NE, NA, not assessable.

Thus clinical evaluation of primary site response can significantly underestimate the rate of CR in SCCHN.

Although survival was not an end point in this trial because of the lack of a defined postchemotherapy treatment plan, a qualitative assessment can be made. With a median follow-up of 21 months and a range 16 to 26 months as of March 2000, nine (21%) of the 43 patients have had disease progression at 6, 7, 8, 9, 9, 10, 13, 13, and 16 months. Six patients have died at 13, 14, 14, 16, 19, and 22 months, two of whom did not have SCCHN. Of the initial 43 patients, 32 (74%) are alive and have no evidence of disease with a minimum follow-up of 16 months. Event-free survival and disease-free survival are shown in Fig 1.

**DISCUSSION**

The present study was designed to establish a safe and tolerable cisplatin dose in combination with docetaxel for induction TPF chemotherapy for SCCHN. TPF is a potential alternative regimen to standard induction PF chemotherapy. A secondary goal was to determine whether there was sufficient activity of the TPF regimen to proceed to phase III testing. The results of this study support the use of cisplatin at 100 mg/m<sup>2</sup> in a regimen of docetaxel, cisplatin, and 5-FU. Toxicity at the higher cisplatin dose was not different from that encountered at the lower dose of 75 mg/m<sup>2</sup>. Toxicity of TPF was generally comparable to historical results with PF with one notable exception, neutropenia.<sup>3,4,23,24</sup> Importantly, the CR rate and the complete pathologic responses observed with this TPF regimen were remarkable in a phase

II setting in very advanced-stage patients and sufficient to justify a randomized comparison with standard PF.

As described above, there was little difference in the systemic or gastrointestinal toxicity with respect to cisplatin dose. There was a questionable increase in the rate of renal-mediated metabolic differences, manifested as a slight increase in the occurrence of severe hypomagnesemia for the higher cisplatin dose. The increased cisplatin dose was also associated with a 10% incidence of significant dehydration. Although TPF was delivered in the outpatient setting, this latter dose-related difference is consistent with standard historical PF regimens and easily controlled with attention to volume requirements. There is a significant difference in hematologic toxicity between TPF and historical PF studies. Although neither PF nor TPF induce significant thrombocytopenia, TPF therapy does result in an early, brief, and consistent neutropenia. This neutropenia is accompanied by brief episodes of febrile neutropenia in 20% of patients, despite prophylactic antibiotics in the majority of patients. The occurrence of episodes of febrile neutropenia in this trial might have been reduced by a more complete compliance with the prophylactic antibiotic therapy mandated by the protocol. Nonetheless, only one patient had a documented serious infection among the 43 patients treated on study. This study suggests that the global toxicity profile of TPF compares favorably with standard PF chemotherapy from historically based, modern phase III trials and is substantially reduced from that seen with TPFL and PFL regimens.<sup>3-5,10,11</sup>

Response data for TPF in this phase I-II trial also compares favorably with that seen with PF in modern, randomized phase III trials.<sup>3-5</sup> The most comparable phase III trials are the VA Larynx Trial, the Studio Trial, and the European Organization for Research and Treatment of Cancer (EORTC) Hypopharynx Trial.<sup>3-5</sup> The overall CR rate and the primary site response rates with TPF are equivalent to or better than the rates seen in these random-

**Table 5. Primary Site Clinical Responses**

	Level I		Level II		All	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
CR	8	62	16	53	24	56
PR	5	38	12	40	17	40
NC	0		1	3	1	2
NA	0		1	3	1	2

**Table 6. Primary Site Pathologic Responses**

Primary Site Clinical Response	Biopsy Result	Level I	Level II	All Patients	
				No. of Patients	%
Biopsy		6/13	19/30	25/43	58
CR	-	3	8	11/12	92
	+	0	1	1/12	8
PR	-	2*	5	7/13	54
	+	1	5	6/13	46

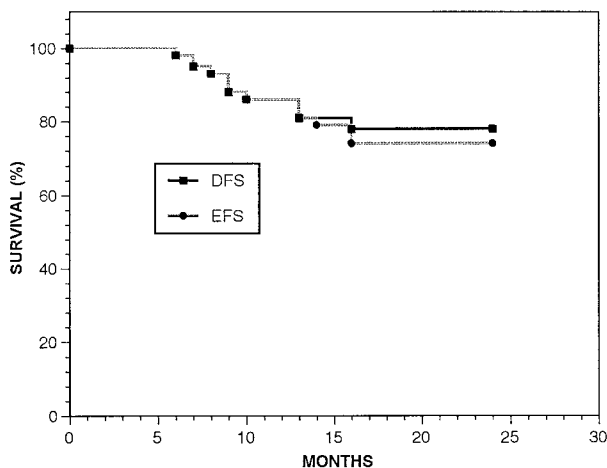
\*One patient had a PR at the primary site, but was rated NC because of a stable neck.

ized trials, despite a TPF-treated population with twice the incidence of advanced nodal presentations compared with the EORTC and VA Larynx studies. The complete clinical response rate at the primary site was 56%. In the VA trial, it seems that 49% of patients experienced a primary site CR and in the EORTC trial 52% had a clinical CR. The pathologic CR rate at the primary sites in TPF is higher than that seen among patients biopsied in the VA Larynx trial. This occurred despite the fact that biopsies in the VA Larynx trial were restricted to a subset of 101 responding patients (72%) from 132 patients treated. Nonresponders in the VA Larynx trial did not have biopsies. Among this selected group of responders, 64% had a negative biopsy. In the current study of TPF, a 72% incidence of negative primary site biopsies was obtained. The negative biopsy rate among PR patients in the VA Larynx Trial was 45% compared with 54% in the TPF trial. Although there is no prospective trial documenting the value of a negative primary site biopsy per se, retrospective data from the VA Larynx trial and data from others suggest that a negative biopsy at the primary site predicts local control and can be

used as a surrogate marker for local control. These data support the notion that TPF is highly effective and warrants comparison with PF as induction chemotherapy in randomized trials for curable, locally advanced SCCHN.

PF has been the standard for induction chemotherapy for organ preservation since the publication of the VA Larynx Trial and the EORTC Hypopharynx Trial. In addition, the Studio Trial demonstrated that induction PF chemotherapy is effective in increasing overall survival in unresectable disease, compared with radiotherapy alone.<sup>5</sup> Unfortunately, as in the Studio Trial, many randomized induction trials have delayed radiotherapy by performing early surgery on resectable and/or postchemotherapy resectable patients.<sup>25,26</sup> By substantially delaying radiotherapy, the potential for tumor repopulation with enhanced resistance in repopulating tumor cells is increased.<sup>27-29</sup> The increased survival in unresectable patients treated with chemotherapy in the Studio Trial occurred in the context of immediate postchemotherapy irradiation followed by postradiotherapy nodal resections rather than early, preradiotherapy surgery. The failure to improve survival in resectable patients in this trial may have been the result of a surgical intervention between chemotherapy and radiotherapy.<sup>30</sup>

Recently, chemoradiotherapy has been demonstrated to be highly effective in increasing survival in patients with unresectable disease in multiple studies, although a direct, well-controlled comparison of standard induction chemotherapy with chemoradiotherapy has not yet been completed.<sup>31-33</sup> Induction chemotherapy and chemoradiotherapy have been established as an appropriate standard of care for many patients with locally advanced SCCHN. Of importance, in a recently published meta-analysis, standard induction PF chemotherapy was as effective as chemoradiotherapy in improving survival in patients with locally advanced disease.<sup>34</sup> In a weighting of the relative benefits of induction chemotherapy versus chemoradiotherapy, induction chemotherapy permits maximum systemic exposure compared with chemoradiotherapy, thereby reducing the risk of inducing partially resistant local and distant tumor cell populations. The toxicity of induction chemotherapy is generally transient and does not compromise the delivery of radiotherapy, whereas the cumulative toxicity of primary chemoradiotherapy reduces the tolerance of patients for postradiation adjuvant chemotherapy. The determination of postchemotherapy response can be used to define the intensity of further treatment. Subsequent, planned sequential chemoradiotherapy after induction chemotherapy and limited surgery postradiotherapy may increase organ preservation, local-regional control, and survival. Induction chemotherapy may be more appropriate than primary che-



**Fig 1. Event-free survival (EFS) and disease-free survival (DFS) for all 43 patients treated with TPF.**

moradiotherapy for treatment for locally advanced SCCHN when it is used in a well-defined, sequential treatment plan.

On the other hand, systemic toxicity is greater with induction chemotherapy; only one trial has shown improved survival relative to radiotherapy alone in unresectable patients; no trials have addressed specifically unresectable patients and compared induction chemotherapy with chemoradiotherapy; induction chemotherapy does not increase local-regional dose-intensity. Given the advantages and disadvantages of induction chemotherapy, a sequential chemotherapy plan in which chemoradiotherapy follows induction therapy might represent the most biologically effective use of both schedules.

This phase I-II trial has demonstrated that TPF induction chemotherapy, with cisplatin at a dose of 100 mg/m<sup>2</sup>, is feasible and safe. The response rates and histologic CR rates are equivalent or better than those seen in randomized PF trials. Because of the established efficacy of standard PF with a cisplatin dose of 100 mg/m<sup>2</sup>, we have recommended this dose of cisplatin be used in phase III trials to maintain maximal dose-intensity.<sup>3-5,34</sup> TPF is now being compared

with PF in a randomized, phase III trial in patients with locally advanced, curable SCCHN. This phase III trial includes protocol-driven sequential chemoradiotherapy with carboplatin and postchemoradiotherapy nodal surgery. The results of this trial will determine whether TPF offers a therapeutic advantage over standard PF and provides a model for future comparisons of sequential chemotherapy with chemoradiotherapy regimens that do not include an induction sequence. Should TPF prove to be better than PF, it would be an appropriate regimen for comparison with chemoradiotherapy regimens exclusively using synchronous therapy or postchemoradiotherapy adjuvant chemotherapy.

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