ORIGINAL ARTICLE

Cisplatin and Fluorouracil Alone or with Docetaxel in Head and Neck Cancer

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ABSTRACT

BACKGROUND

A randomized phase 3 trial of the treatment of squamous-cell carcinoma of the head and neck compared induction chemotherapy with docetaxel plus cisplatin and fluorouracil (TPF) with cisplatin and fluorouracil (PF), followed by chemoradiotherapy.

METHODS

We randomly assigned 501 patients (all of whom had stage III or IV disease with no distant metastases and tumors considered to be unresectable or were candidates for organ preservation) to receive either TPF or PF induction chemotherapy, followed by chemoradiotherapy with weekly carboplatin therapy and radiotherapy for 5 days per week. The primary end point was overall survival.

RESULTS

With a minimum of 2 years of follow-up (≥3 years for 69% of patients), significantly more patients survived in the TPF group than in the PF group (hazard ratio for death, 0.70; P=0.006). Estimates of overall survival at 3 years were 62% in the TPF group and 48% in the PF group; the median overall survival was 71 months and 30 months, respectively (P=0.006). There was better locoregional control in the TPF group than in the PF group (P=0.04), but the incidence of distant metastases in the two groups did not differ significantly (P=0.14). Rates of neutropenia and febrile neutropenia were higher in the TPF group; chemotherapy was more frequently delayed because of hematologic adverse events in the PF group.

CONCLUSIONS

Patients with squamous-cell carcinoma of the head and neck who received docetaxel plus cisplatin and fluorouracil induction chemotherapy plus chemoradiotherapy had a significantly longer survival than did patients who received cisplatin and fluorouracil induction chemotherapy plus chemoradiotherapy. (ClinicalTrials.gov number, NCT00273546.)

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Squamous-cell carcinoma of the head and neck accounts for 5% of newly diagnosed cancers in adults in the United States and 8% of cancers worldwide.[1] The disease is potentially curable at an early stage, but most patients present with locally advanced disease. After standard therapy (surgery and irradiation), only 30 to 50% of patients with locally advanced disease live for 3 years, and locoregional recurrences or distant metastases develop in 40 to 60% of them.[2-6] Various strategies to improve outcomes by coordinating chemotherapy with surgery and radiotherapy have been tried, but the optimal schedule for integrating chemotherapy into the management of this disease has yet to be defined.[7]

Although chemoradiotherapy (radiotherapy plus concurrent chemotherapy) has become the standard of care for patients with unresectable squamous-cell carcinoma of the head and neck[2] and for organ preservation,[3,8] induction chemotherapy with cisplatin and fluorouracil (PF) also has benefits in this disease.[9-11] A comprehensive meta-analysis showed that induction chemotherapy (i.e., chemotherapy as the initial treatment) with PF significantly improved the rate of survival at 5 years, as compared with standard radiotherapy plus surgery in patients with locally advanced disease.[11]

Docetaxel (Taxotere, Sanofi-Aventis) has substantial activity when administered alone in patients with recurrent or incurable disease.[12,13] In phase 1 and phase 2 studies of docetaxel plus cisplatin and fluorouracil (TPF) in the treatment of locally advanced squamous-cell carcinoma of the head and neck, including phase 2 studies of treatment with curative intent, clinical and pathological response rates have been high and survival has been prolonged.[14-18] Two phase 3 trials in which induction chemotherapy with TPF or PF was followed by radiotherapy (the European Organization for Research and Treatment of Cancer [EORTC] 24971/TAX 323 study by Vermorken et al.[19]) or chemoradiotherapy (TAX 324) in locally advanced disease have now been completed. The results of the study by Vermorken et al. are reported in this issue of the *Journal*. We report on the results of the TAX 324 study here.

METHODS

PATIENTS

Patients who had measurable, nonmetastatic, histologically proven stage III or IV squamous-cell carcinoma of the oral cavity, larynx, oropharynx, or hypopharynx were eligible if the tumor was deemed to be either unresectable (because of tumor fixation, involvement of the nasopharynx, or fixed lymph nodes) or of low surgical curability on the basis of advanced tumor stage (3 or 4) or regional-node stage (2 or 3, except T1N2), or if the patient was a candidate for organ preservation. Patients had to be at least 18 years of age with a World Health Organization (WHO) performance status of 0 or 1 and adequate bone marrow, liver, and renal function. Exclusion criteria were any previous chemotherapy or radiotherapy, a cancer diagnosis within the previous 5 years, another active cancer, any previous definitive surgery for squamous-cell carcinoma of the head and neck, severe weight loss (>20% of body weight) in the preceding 3 months, and chronic obstructive pulmonary disease requiring hospitalization within the previous 12 months.

Disease was staged according to the criteria of the American Joint Committee on Cancer.[20] All patients provided written informed consent, and each study center was required to have approval from its institutional review board before randomization.

STUDY DESIGN

In a randomized, open-label phase 3 trial, we compared three cycles of TPF induction chemotherapy with three cycles of PF induction chemotherapy; both regimens were followed by 7 weeks of chemoradiotherapy (Fig. 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). Randomization was performed centrally with the use of a biased-coin minimization technique. At study entry, patients were stratified according to the site of the primary tumor, nodal status (N0 or N1 vs. N2 or N3), and institution. Patients with progressive disease after induction chemotherapy or chemoradiotherapy were treated according to the institution's choice of salvage therapy (Fig. 1 of the Supplementary Appendix). Neck dissections were performed after the completion of chemoradiotherapy. The primary end point was overall survival. Secondary end points included progression-free survival, response rates after induction chemotherapy, and toxic effects.

One of the academic investigators designed, wrote, and implemented the study protocol and managed the study in collaboration with employees of the sponsor, Sanofi-Aventis. Lead investiga-

tors from each center collected the data and ensured its accuracy and completeness. Statistical analysis was performed by industry representatives. Dr. Posner wrote the manuscript, which was reviewed by the coauthors; determined its final content; and vouches for its completeness and accuracy.

TREATMENT

Induction Chemotherapy

For patients who were randomly assigned to receive TPF, docetaxel (at a dose of 75 mg per square meter of body-surface area) was administered as a 1-hour intravenous infusion, followed by intravenous cisplatin (100 mg per square meter), administered during a period of 0.5 to 3 hours. After completion of the cisplatin infusion, fluorouracil (1000 mg per square meter per day) was administered as a continuous 24-hour infusion for 4 days. Patients in the PF group received intravenous cisplatin (100 mg per square meter), followed by fluorouracil (1000 mg per square meter per day) as a continuous 24-hour infusion for 5 days. Induction chemotherapy was given every 3 weeks for three cycles, unless there was disease progression, unacceptable toxic effects, withdrawal of consent by the patient, or a reduction of less than 25% in tumor size after cycle 2. Patients in the TPF group were given dexamethasone to prevent docetaxel-related hypersensitivity reactions, skin toxic effects, and fluid retention and were given prophylactic antibiotics starting on day 5 of each cycle for 10 days. Primary prophylaxis with recombinant granulocyte colony-stimulating factor was not permitted.

Chemoradiotherapy

All patients were assigned to receive chemoradiotherapy beginning 3 to 8 weeks after the start of the third cycle of induction chemotherapy (day 22 to day 56 of cycle 3). Weekly carboplatin at an area under the curve of 1.5 was given as an intravenous infusion during a 1-hour period for a maximum of seven weekly doses during the course of radiotherapy.[21-24]

The definitive curative radiation dose administered to the primary tumor was between 70 and 74 Gy, administered as fractions of 2 Gy per day 5 days per week. The dose administered to uninvolved lymph nodes was at least 50 Gy. Involved lymph nodes were to receive 60 to 74 Gy, depending on whether an elective neck dissection was indicated after completion of treatment. Quality assurance for radiotherapy involved central review at both the initiation and the completion of such treatment.

Surgery

Surgery was performed 6 to 12 weeks after completion of chemoradiotherapy for patients who had an initial nodal stage of N2 and a partial response to induction chemotherapy, N3 disease, or residual disease after chemoradiotherapy. Surgery was also allowed for patients who did not complete chemoradiotherapy and had resectable residual disease at the primary site or in the neck.

ASSESSMENTS AND OUTCOMES

A complete medical history was obtained and tumor assessment was performed at baseline. Tumor responses were assessed by clinical evaluation and imaging studies and were characterized according to modified WHO criteria after cycles 2 and 3 of induction chemotherapy, 6 to 12 weeks after the completion of chemoradiotherapy, and during follow-up visits until disease progression.

Overall survival was calculated from the date of randomization to the date of death; progression-free survival was calculated from randomization to progression or death from any cause, whichever occurred first. Patients were monitored monthly for recurrence in the first year, every 2 months in the second year, every 3 months in the third year, and every 6 months thereafter until death or data censoring. Follow-up ended at the completion of the trial (2 years after the last patient underwent randomization).

Toxic effects were assessed weekly during induction chemotherapy, during and on completion of chemoradiotherapy, and at subsequent predefined intervals. We used the Common Toxicity Criteria (1994 version) of the Clinical Trials Group of the National Cancer Institute of Canada and the criteria of the Radiation Therapy Oncology Group of the EORTC for acute and late toxic effects of radiation.

STATISTICAL ANALYSIS

The study had a power of 91% to detect a hazard ratio for death of 0.65 on the basis of an assumed median survival of 43 months in the TPF group and 28 months in the PF group, with use of a two-sided log-rank test at a level of significance of 0.05. A minimum follow-up of 24 months and a total of 227 events were required. A maximum of 250 patients per group were to be recruited on

the assumption that 15% would drop out early or be lost to follow-up.

The null hypothesis of no difference in progression-free survival between study groups was tested with the use of the log-rank test at a two-sided level of significance of 0.05. To achieve a power of 90%, assuming a true median progression-free survival of 15 months in the TPF group and 10 months in the PF group, a total of 256 events were needed. With 218 patients enrolled per treatment group, a minimum follow-up of 3 months and 30 months of accrual were needed to achieve this target.

The analysis of survival was conducted in the intention-to-treat population with the use of the Kaplan–Meier method. Confidence intervals were calculated for median survival according to the method of Brookmeyer and Crowley.[25] Hazard ratios were calculated with the use of the Cox proportional-hazards model. Study groups were compared by means of the log-rank test. All treated patients were included in the analysis of adverse events. All other hypothesis testing was two-sided at a significance level of 0.05.

RESULTS

PATIENTS

Between May 21, 1999, and December 3, 2003, a total of 539 patients from 55 centers in the United States, Canada, Argentina, and Europe were enrolled. The cutoff date for the analysis of overall survival was December 3, 2005, corresponding to 2 years of follow-up for the last patient enrolled in the study. As a result of a computer error in randomization, 37 patients were excluded from the intention-to-treat population, and 1 patient was excluded owing to a violation in Good Clinical Practice guidelines.

Table 1 shows demographic and tumor characteristics of the 501 patients who underwent randomization — 255 in the TPF group and 246 in the PF group — in the intention-to-treat population. More than 80% of the patients were men, and the predominant primary site of disease was the oropharynx. After randomization, the TPF group included more patients with T4 lesions than did the PF group (49% vs. 37%, P=0.04); the characteristics of the patients were otherwise well balanced between the two groups.

TREATMENT

Of a total of 501 patients, 494 (99%) started induction chemotherapy (Table 2). Most patients completed the induction chemotherapy and started chemoradiotherapy; 68 patients in the TPF group (27%) and 79 patients in the PF group (32%) discontinued study treatment, primarily because of progressive disease. The percentage of patients who discontinued treatment because of adverse events was similar in the two groups.

EFFICACY

At the time of the last analysis, patients had been followed for a minimum of 24 months and a median of 42 months; 69% of patients were followed for at least 3 years. Treatment with TPF resulted in a 30% reduction in the risk of death (hazard ratio 0.70; 95% confidence interval [CI], 0.54 to 0.90; P=0.006) (Fig. 1A and Table 3). Median survival was 71 months (95% CI, 49 to not reached) in the TPF group and 30 months (95% CI, 21 to 52) in the PF group (P=0.006). Estimated 3-year survival was 62% (95% CI, 56 to 68) in the TPF group and 48% (95% CI, 42 to 55) in the PF group (P=0.002). Overall, 234 patients (47%) had died as of the cutoff date: 104 patients (41%) in the TPF group and 130 (53%) in the PF group. Tumor progression was the most common cause of death (occurring in 29% of the TPF group and in 41% of the PF group, P=0.34).

Treatment with TPF was associated with a trend toward improved survival in all subgroups of patients, including those with an advanced nodal stage and primary tumor stage or any level of resectability (Table 3). Among patients with resectable tumors who were candidates for organ preservation, the median survival was not reached in the TPF group; the PF group had a median survival of 42 months (hazard ratio, 0.52; 95% CI, 0.32 to 0.84; P=0.007). In patients with unresectable tumors, median survival was 40 months in the TPF group and 21 months in the PF group (hazard ratio, 0.68; 95% CI, 0.45 to 1.01; P=0.06).

As compared with the PF group, the TPF group had a significant reduction in the risk of disease progression or death (hazard ratio, 0.71; 95% CI, 0.56 to 0.90; P=0.004) (Fig. 1B and Table 3). The median progression-free survival was 36 months (95% CI, 19 to not reached) in the TPF group and 13 months (95% CI, 11 to 20) in the PF group.

Table 1. Characteristics of the Patients.*

Variable	TPF (N=255)	PF (N=246)	P Value†
Age — yr			0.30‡
Median	55	56	
Range	38–82	33–80	
Sex — no. (%)			0.72
Male	215 (84)	204 (83)	
Female	40 (16)	42 (17)	
WHO performance status — no. (%)			0.16
0	142 (56)	126 (51)	
1	113 (44)	117 (48)	
Unknown	0	3 (1)	
Site of primary tumor — no. (%)			0.68
Hypopharynx	43 (17)	34 (14)	
Larynx	47 (18)	42 (17)	
Oral cavity	33 (13)	38 (15)	
Oropharynx	132 (52)	131 (53)	
Other	0	1 (<1)	
Stage of primary tumor — no. (%)			0.04
T1	13 (5)	9 (4)	
T2	43 (17)	56 (23)	
T3	74 (29)	88 (36)	
T4	125 (49)	92 (37)	
TX§	0	1 (<1)	
Nodal stage — no. (%)			0.74
N0	42 (16)	35 (14)	
N1	53 (21)	49 (20)	
N2	128 (50)	123 (50)	
N3	32 (13)	38 (15)	
NX¶	0	1 (<1)	
Overall stage of disease — no. (%)			0.48
III	41 (16)	46 (19)	
IV	214 (84)	199 (81)	
Unknown	0	1 (<1)	
Reason for inoperability — no. (%)			0.86
Technical unresectability	92 (36)	84 (34)	
Low surgical curability	78 (31)	75 (30)	
Organ preservation	85 (33)	87 (35)	

* PF denotes cisplatin and fluorouracil, TPF docetaxel plus cisplatin and fluorouracil, and WHO World Health Organization. Percentages may not total 100 because of rounding.
† P values were determined by Fisher's exact test.
‡ The P value is for the comparison between patients less than 60 years of age and those 60 years or older.
§ One patient in the PF group underwent excisional biopsy of the primary tumor that was not staged.
¶ One patient in the PF group underwent diagnostic surgery for nodal disease that was not staged.

Table 2. Treatment Received and Reasons for Discontinuation.*

Variable	TPF (N=255)	PF (N=246)
	no. (%)	
Chemotherapy	251 (98)	243 (99)
Chemoradiotherapy	202 (79)	184 (75)
Completion of study treatment per protocol	187 (73)	167 (68)
Discontinuation of study treatment	68 (27)	79 (32)
Reason for discontinuation		
Progressive disease	17 (7)	31 (13)
Adverse event	19 (7)	19 (8)
Not related to treatment	4 (2)	0
Related to treatment	15 (6)	17 (7)
Not recorded	0	2 (1)
Death	4 (2)	6 (2)
From cancer	0	1 (<1)
From toxic effect of study drug	1 (<1)	1 (<1)
Other	3 (1)	4 (2)
Consent withdrawn	12 (5)	7 (3)
Other	16 (6)	16 (6)

* PF denotes cisplatin and fluorouracil, and TPF docetaxel plus cisplatin and fluorouracil.

Figure 1 (facing page). Overall Survival and Progression-free Survival.

Panel A shows the Kaplan–Meier estimates of overall survival among the 501 patients in the intention-to-treat population who were randomly assigned to induction chemotherapy with TPF or PF. The hazard ratio for death in the TPF group as compared with the PF group was 0.70 (95% CI, 0.54 to 0.90; P=0.006 by the log-rank test). Median survival in the TPF group was 71 months (95% CI, 49 to not reached), as compared with 30 months (95% CI, 21 to 52) in the PF group. Panel B shows the Kaplan–Meier estimates of progression-free survival among the 501 patients in the intention-to-treat population. The hazard ratio for disease progression in the TPF group as compared with the PF group was 0.71 (95% CI, 0.56 to 0.90; P=0.004 by the log-rank test). Median progression-free survival in the TPF group was 36 months (95% CI, 19 to not reached) and 13 months in the PF group (95% CI, 11 to 20). The points on the curves show when data for patients were censored. PF denotes cisplatin and fluorouracil, and TPF docetaxel plus cisplatin and fluorouracil.

Estimates of progression-free survival at 2 years were 53% in the TPF group and 42% in the PF group (P=0.01).

At the time of this analysis, the treatment had failed in 198 patients, 88 (35%) in the TPF group and 110 (45%) in the PF group (P=0.01) (Table 3). Nineteen patients had second primary tumors. The rate of reported locoregional failure was 30% in the TPF group and 38% in the PF group (P=0.04). Distant metastases occurred in 5% and 9% of the patients, respectively (P=0.14).

The overall response rate after induction chemotherapy was 72% in the TPF group and 64% in the PF group (P=0.07) (Table 1 of the Supplementary Appendix). The percentages of patients with a complete response were similar in the two groups (17% in the TPF group and 15% in the PF group, P=0.66).

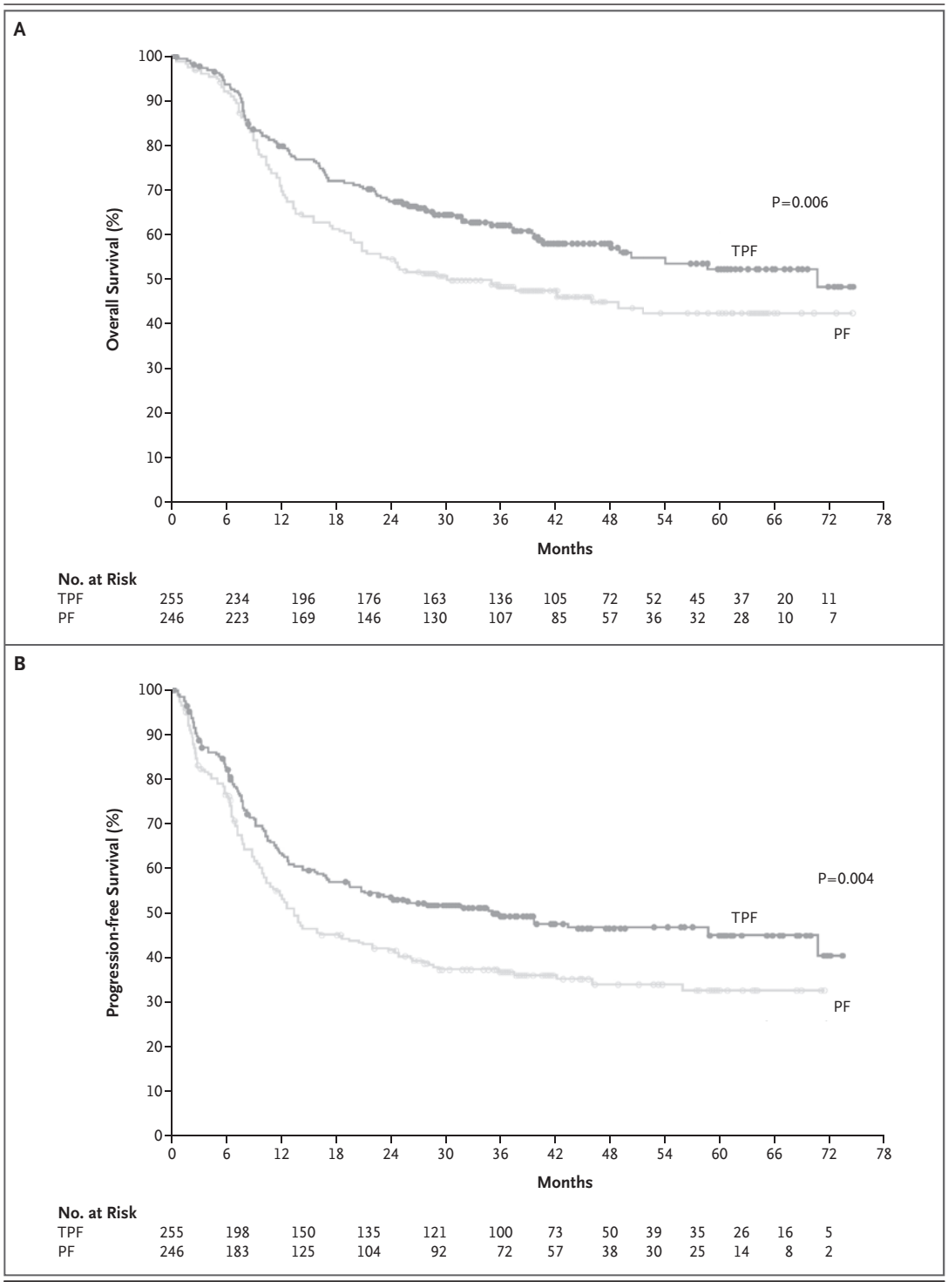
ADVERSE EVENTS

Of the 494 patients who received induction chemotherapy, 491 (99%) had at least one treatment-related adverse event. Grade 3 or 4 neutropenia occurred in 83% of patients in the TPF group and in 56% of patients in the PF group (P<0.001) (Table 4). Despite antibiotic prophylaxis, rates of febrile neutropenia and neutropenic infection were higher in the TPF group. The percentages of patients with grade 3 or 4 anemia were similar in the two groups. Grade 3 or 4 thrombocytopenia was more frequent in the PF group than in the TPF group (11% vs. 4%, P=0.005).

Patients in the TPF group had fewer treatment delays than did those in the PF group (29% vs. 65%, P<0.001), despite differences in peak myelotoxicity during induction chemotherapy in the TPF group. Prolonged neutropenia accounted for the difference and was responsible for treatment-associated delays in 1% of patients in the TPF group and 39% of patients in the PF group (P<0.001) (Table 4). The percentage of planned treatments that patients received was 98% in the TPF group and 90% in the PF group (Table 2 of the Supplementary Appendix). Thus, neutropenia was less likely to affect dose delivery and treatment cycles in the TPF group than in the PF group.

Rates of grade 3 or 4 nonhematologic toxic effects were similar in the two study groups (65% in the TPF group and 62% in the PF group). Except for a significant difference in grade 3 or 4 lethargy and a nonsignificant difference in mucositis, which were reported more often in the PF group, there were no major differences in nonhematologic adverse events in the two groups during induction chemotherapy (Table 4, and Table 3 of the Supplementary Appendix).

No significant differences in the rates of adverse events were observed during chemoradio-



therapy (Table 4, and Table 4 of the Supplementary Appendix). There were no significant differences in the doses of radiotherapy and chemotherapy delivered to each group during chemoradiotherapy (Table 5 of the Supplementary Appendix).

DISCUSSION

The results of this randomized trial of therapy for locally advanced squamous-cell carcinoma of the head and neck show the advantages of induc-

Table 3. Antitumor Efficacy.*

Variable	TPF (N=255)	PF (N=246)	Hazard Ratio (95% CI)†	P Value‡
Overall survival§				
Median duration — mo	71	30	0.70 (0.54–0.90)	0.006
Rate — %				
At 2 yr	67	55		
At 3 yr	62	48		
Median duration according to site of primary tumor — mo				
Oropharynx	NR	NR	0.70 (0.47–1.03)	0.07
Hypopharynx	32	20	0.67 (0.37–1.20)	0.18
Larynx	59	25	0.58 (0.32–1.04)	0.07
Oral cavity	37	14	0.87 (0.47–1.60)	0.66
Median duration according to resectability — mo				
Technical unresectability	40	21	0.68 (0.45–1.01)	0.06
Low surgical curability	NR	49	0.89 (0.56–1.41)	0.61
Organ preservation	NR	42	0.52 (0.32–0.84)	0.007
Median duration according to disease stage — mo				
III	71	51	0.50 (0.24–1.05)	0.07
IV	59	25	0.72 (0.55–0.95)	0.02
Median duration according to primary tumor stage — mo				
T3	71	46	0.74 (0.46–1.18)	0.21
T4	32	21	0.82 (0.57–1.17)	0.26
Median duration according to nodal stage — mo				
N2	NR	46	0.79 (0.54–1.15)	0.21
N3	37	12	0.60 (0.33–1.09)	0.10
Progression-free survival				
Median duration — mo	36	13	0.71 (0.56–0.90)	0.004
Rate — %				
At 2 yr	53	42		
At 3 yr	49	37		
Time to progression				
Median duration — mo	NR	14	0.66 (0.50–0.86)	0.002
Rate — %				
At 2 yr	57	43		
At 3 yr	54	40		
Site of treatment failure				
Patients with treatment failure — no. (%)	88 (35)	110 (45)	0.70 (0.53–0.92)	0.01
Locoregional failure — no. (%)	77 (30)	93 (38)	0.73 (0.54–0.99)	0.04
Primary	43 (17)	49 (20)		
Neck	22 (9)	33 (13)		
Both	12 (5)	11 (4)		
Distant metastases — no. (%)	14 (5)	21 (9)	0.60 (0.30–1.18)	0.14
Distant only	11 (4)	17 (7)		
Distant and locoregional	3 (1)	4 (2)		
Second primary tumors — no. (%)	9 (4)	10 (4)		

* PF denotes cisplatin and fluorouracil, TPF docetaxel plus cisplatin and fluorouracil, and NR not reached.
† Hazard ratios are for death in the TPF group as compared with the PF group. Outcomes were as follows: death (in the analysis of overall survival), progression or death (in the analysis of progression-free survival), progression or death within 100 days before further therapy (in the analysis of time to progression), and locoregional recurrence (in the analysis of the site of locoregional failure).
‡ P values were calculated by the log-rank test.
§ The median follow-up was 41 months in the TPF group and 42 months in the PF group.

Table 4. Adverse Events and Treatment Delays.*

Variable	TPF	PF	P Value†
Adverse events during induction chemotherapy			
No. of patients	251	243	
Hematologic — %			
Anemia grade 3 or 4	12	9	0.32
Thrombocytopenia grade 3 or 4	4	11	0.005
Neutropenia grade 3 or 4‡	83	56	<0.001
Febrile neutropenia‡§	12	7	0.04
Neutropenic infection¶	12	8	0.23
Nonhematologic grade 3 or 4 — %			
Stomatitis (mucositis)	21	27	0.14
Nausea	14	14	1.00
Esophagitis, dysphagia, or odynophagia	13	9	0.26
Anorexia	12	12	0.78
Vomiting	8	10	0.54
Diarrhea	7	3	0.07
Infection	6	5	0.70
Lethargy	5	10	0.03
Treatment delays during induction chemotherapy‖			
No. of patients	251	243	
Patients who had delays — no. (%)	73 (29)	157 (65)	<0.001
Reason for delay			
Hematologic			
Any adverse event	11 (4)	108 (44)	<0.001
Neutropenia	2 (1)	95 (39)	
Nonhematologic	25 (10)	22 (9)	0.76
Other**	38 (15)	40 (16)	0.71
Adverse events during chemoradiotherapy			
No. treated with chemoradiotherapy	202	184	
Nonhematologic grade 3 or 4 — %			
Stomatitis (mucositis)	37	38	1.00
Esophagitis, dysphagia, or odynophagia	23	24	0.81
Anorexia	11	15	0.29
Infection	9	7	0.45
Lethargy	6	6	1.00
Nausea	6	6	1.00
Vomiting	3	5	0.46
Diarrhea	0	2	0.11

* Adverse events are listed regardless of whether they were associated with treatment. Major adverse events are shown; see the tables in the Supplementary Appendix for a complete list. PF denotes cisplatin and fluorouracil, and TPF docetaxel plus cisplatin and fluorouracil.
† P values were calculated by Fisher's exact test.
‡ Percentages are based on the number of patients who could be evaluated for neutropenia (248 in the TPF group and 241 in the PF group).
§ Febrile neutropenia was defined as fever of grade 2 or more concomitant with grade 4 neutropenia requiring intravenous antibiotics, hospitalization, or both.
¶ Neutropenic infection was defined as infection of grade 2 or more concomitant with grade 3 or 4 neutropenia.
‖ A patient may have had a delay in treatment because of one or more adverse events.
** Other reasons for treatment delays included logistics, personal reasons, and vacations.

tion TPF chemotherapy followed by chemoradiotherapy over induction PF followed by chemoradiotherapy. Longer overall and progression-free survival and a nonsignificant reduction in overall toxic effects were evident in the TPF group. At a median follow-up of 42 months, TPF reduced the risk of death by 30%, as compared with PF, with estimated 3-year survival rates of 62% in the TPF group and 48% in the PF group (P=0.002). A consistent survival benefit was observed in subgroup analyses across all primary tumor sites and advanced nodal stages, but the difference was not statistically significant. Patients in the TPF group had a significant reduction in reported locoregional failure, but as compared with PF, the effect of TPF on distant metastases did not differ significantly. Treatment with TPF was associated with a nonsignificant decrease in mucositis, and although there was more myelotoxicity in the TPF group than in the PF group, there were significantly fewer treatment delays in the TPF group, reflecting reduced overall toxic effects.

PF induction chemotherapy improves survival in unresectable squamous-cell carcinoma of the head and neck[9-11] and is effective as organ-preserving therapy for the larynx and hypopharynx.[4,5,8,26] However, chemoradiotherapy has become the standard of care for definitive therapy of locally advanced disease in North America.[2,8,27] A recent analysis of the only phase 3 study that has compared induction chemotherapy, chemoradiotherapy, and radiotherapy alone reported that PF induction chemotherapy was equivalent to cisplatin-based chemoradiotherapy, and both were significantly better than radiotherapy alone in terms of 5-year survival with an intact larynx.[4] Overall survival was better with PF induction, but it did not differ significantly from survival with chemoradiotherapy or radiotherapy.[4]

The sequential design of the TAX 324 trial was based on outcomes of previous phase 2 and phase 3 studies that used intensive induction strategies followed by radiotherapy alone; in these trials there were significant numbers of locoregional failures but few distant metastases.[17] Studies of chemoradiotherapy alone showed that it was associated with lower rates of locoregional failure than was radiotherapy alone but with a minimal effect on the rate of distant metastases.[2,3,6,28,29] Therefore, TAX 324 incorporated both induction chemotherapy and chemoradiotherapy in an attempt to improve locoregional control, eliminate distant metastases, and improve survival. We found that induction with TPF reduced the risk of locoregional failure by 27%, as compared with PF, yet locoregional failure remained the single most important cause of treatment failure. In both groups, distant metastases were infrequent and fewer than would be expected with chemoradiotherapy. Previous studies of induction therapy in resectable and unresectable squamous-cell carcinoma of the head and neck have suggested that induction chemotherapy is most effective in unresectable disease.[9,10] This observation may have been in part a function of scheduling surgery between chemotherapy and radiotherapy in patients with resectable tumors. In our study, subgroup analyses showed that in the TPF group there was a consistent trend toward improved survival, regardless of the primary site of disease, reason for therapy, nodal status, primary tumor stage, and surgical curability.

In the study by Vermorken et al., a similar TPF induction regimen was compared with PF followed by radiotherapy alone in patients with unresectable tumors. This trial also demonstrated that TPF improved survival with an acceptable toxicity profile.[19,30] The results of both phase 3 induction trials support the conclusion that TPF combinations are appropriate for induction chemotherapy.

Ongoing phase 3 comparisons of sequential therapy with chemoradiotherapy alone may establish which of these two approaches is superior.[7] Until those trials have been completed, clinicians should consider TPF-based sequential therapy to be a reasonable alternative to chemoradiotherapy alone in patients with locally advanced disease.

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APPENDIX

In addition to the authors, the following investigators participated in the TAX 324 study: *Hospital Evito, Rio de Janeiro* — M. Freue; *University of Medicine and Dentistry of New Jersey, Newark* — L. Pliner; *William Jennings Bryan Dorn Veteran Affairs Medical Center, Columbia, SC* — W. Hrushesky; *Providence Medical Center, Southfield, MI* — A. Drelichman; *Carolina Hematology Oncology Associates, Charlotte, NC* — G. Frenette; *Instituto Portugues de Oncologia Francisco Gentil, Porto, Portugal* — M. Lopes; *Washington University School of Medicine, St. Louis* — D. Adkins; *Corpus Christi Cancer Center, Corpus Christi, TX* — A. Wood; *Louisiana State University Health Sciences Center, Shreveport* — G. Mills; *Veterans Affairs Medical Center, San Juan, Puerto Rico* — L. Baez; *European Hospital Georges Pompidou, Paris* — M. Housset; *Central Research Institute for Radiology, St. Petersburg, Russia* — N. Ilyan; *Veteran Affairs Medical Center, Atlanta* — M. Ribeiro; *Florida Cancer Institute, Port Richey* — G. Robbins; *Metro Nashville General Hospital, Nashville* — E. Ikpeazu; *Veterans Affairs Medical Center, Washington, DC* — S. Krasnow; *Akron General Medical Center, Akron, OH* — J. Petrus; *Centre René Gaudducheau, Saint Herblain, France* — F. Rolland; *Fallon Clinic, Worcester, MA* — C. Seidler; *University of Florida–Jacksonville, Jacksonville* — T. Guthrie.

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