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ORIGINAL REPORT

Tirapazamine, Cisplatin, and Radiation Versus Fluorouracil, Cisplatin, and Radiation in Patients With Locally Advanced Head and Neck Cancer: A Randomized Phase II Trial of the Trans-Tasman Radiation Oncology Group (TROG 98.02)

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ABSTRACT

Purpose
To select one of two chemoradiotherapy regimens for locally advanced squamous cell carcinoma (SCC) of the head and neck as the experimental arm for the next Trans-Tasman Radiation Oncology Group phase III trial.

Patients and Methods
One hundred twenty-two previously untreated patients with stage III/IV SCC of the head and neck were randomized to receive definitive radiotherapy (70 Gy in 7 weeks) concurrently with either cisplatin (75 mg/m^2) plus tirapazamine (290 mg/m^2/d) on day 2 of weeks 1, 4, and 7, and tirapazamine alone (160 mg/m^2/d) on days 1, 3, and 5 of weeks 2 and 3 (TPZ/CIS), or cisplatin (50 mg/m^2) on day 1 and infusional fluorouracil (360 mg/m^2/d) on days 1 through 5 of weeks 6 and 7 (chemoboost).

Results
Three-year failure-free survival rates were 55% with TPZ/CIS (95% CI, 39% to 70%) and 44% with chemoboost (95% CI, 30% to 60%; log-rank $P = .16$). Three-year locoregional failure-free rates were 84% in the TPZ/CIS arm (95% CI, 71% to 92%) and 66% in the chemoboost arm (95% CI, 51% to 79%; $P = .069$). More febrile neutropenia and grade 3 or 4 late mucous membrane toxicity were observed with TPZ/CIS, while acute skin radiation reaction was more severe and prolonged with chemoboost. Compliance with protocol treatment was satisfactory on both arms.

Conclusion
Both regimens are feasible and are associated with significant but acceptable toxicity profiles in the cooperative group setting. Based on the promising efficacy seen in this trial, TPZ/CIS is being evaluated in a large phase III trial.

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INTRODUCTION

Adding concurrent platinum-based chemotherapy to radiation has been demonstrated to improve locoregional control, disease-free survival, organ preservation, and overall survival in patients with locoregionally advanced head and neck cancer.[1-6] The choice of doses and scheduling of the chemotherapy has been largely empirical.

The concomitant boost radiotherapy regimen was developed to offset accelerated repopulation, by reducing treatment duration without sacrificing total dose.[7] A randomized phase II study[8] demonstrated that the optimal time to give the boost was

during the last 2 weeks of wide field treatment. A subsequent phase III trial showed that concomitant boost radiotherapy was superior to conventionally fractionated radiotherapy.[9] It was subsequently hypothesized, based on extrapolation from the radiotherapy results, that concomitant chemotherapy may be most effective when given as a form of dose intensification toward the end of radiotherapy, which led to the development of the chemoboost regimen. Promising results with this regimen have been reported in phase II trials.[10,11]

The potential importance of hypoxia as a mechanism limiting the cure rate in patients with head and neck cancer treated with radiation has been recognized for a long time.[12] In recent years, a conceptually new approach to tumor hypoxia has been developed using tirapazamine, a drug that is preferentially cytotoxic to hypoxic cells. Preclinical studies have demonstrated that tirapazamine results in potentiation of both radiation and cisplatin cytotoxicity.[13,14] In a phase I trial of tirapazamine, cisplatin, and radiation (TPZ/CIS), impressive results were seen in a group of patients with T3/4 and/or N2/N3 head and neck cancer.[15]

In the Trans-Tasman Radiation Oncology Group (TROG) 98.02 randomized phase II trial, we sought to test two promising chemoradiotherapy strategies, one based on tumor hypoxia, the other based on repopulation kinetics, in the multicenter cooperative group setting. The primary objective was to choose one of these regimens as the experimental arm for the next TROG phase III trial, based on feasibility, protocol compliance, acceptable toxicity, and promising efficacy.

PATIENTS AND METHODS

Study Design and Eligibility

This study was an open-label, randomized phase II trial studying two concurrent chemoradiotherapy regimens. The trial was conducted under the auspices of TROG in 13 centers across Australia and New Zealand.

Patient eligibility criteria included: previously untreated squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx; stage III or IV disease (excluding T1N1 and distant metastases); age $\geq$ 18 years; Eastern Cooperative Oncology Group performance status 0 to 2; adequate hematologic, renal, and liver function; no prior radiotherapy for head and neck cancer; no prior cisplatin use; no concurrent active cancer in the last 5 years except treated nonmelanoma skin cancer or cervical dysplasia; no history of unstable cardiac disease; and no peripheral neuropathy $\geq$ grade 2. Written informed consent was obtained from all patients and the Institutional Ethics Committees approved the protocol.

Pretreatment and Follow-Up Evaluations

Before enrollment onto the trial, all patients underwent a full medical history and physical examination, blood tests, computed tomography (CT) or magnetic resonance imaging of the head and neck, and chest x-ray (CT of the chest if patient's low neck nodes were involved). Assessment of tumor response by clinical examination and CT scanning took place at 12 weeks and 26 weeks after completion of treatment.

Systemic toxicity from treatment was graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Acute radiation toxicities were graded according to the European Organisation for Research and Treatment of Cancer Radiation Therapy Oncology Group (EORTC-RTOG) toxicity criteria. Radiation toxicities occurring more than 90 days after starting radiation were graded according to the EORTC-RTOG late toxicity criteria. The only exception was mucositis, which continued to be graded as an acute effect beyond 90 days after treatment, until graded to be less than grade 2.

Treatment Plan

Arm 1. Tirapazamine was supplied by Sanofi-Synthelabo pharmaceuticals (Sydney, Australia). On day 2 of weeks 1, 4, and 7, tirapazamine 290 mg/m^2 was administered for 2 hours, followed 1 hour later by cisplatin 75 mg/m^2 for 1 hour, followed immediately by radiotherapy. In addition, tirapazamine 160 mg/m^2 was given before radiation three times a week in weeks 2 and 3. When tirapazamine was administered without cisplatin, radiotherapy was given no earlier than 30 minutes and no later than 120 minutes after the end of the tirapazamine infusion. Prophylactic recombinant granulocyte colony-stimulating factor (G-CSF) support was not permitted.

Arm 2. Cisplatin 50 mg/m^2 was given before radiotherapy on day 1 of weeks 6 and 7 of radiotherapy. Fluorouracil 360 mg/m^2/d was given by continuous infusion from day 1 through day 5 (120-hour infusion) of weeks 6 and 7 of radiotherapy.

Radiation Therapy

Both arms received 70 Gy of planned radiation therapy in 35 fractions for 7 weeks. The radiation was given using a shrinking field technique. The initial 50 Gy encompassed the gross clinical disease and sites suspected of harboring subclinical disease. The maximal spinal cord dose was 45 Gy. The fields were then reduced in size to 70 Gy to treat the areas of gross macroscopic disease, with a buffer zone of 60 Gy around larger nodal masses.

Dose Modification for Toxicity

If grade 3 or 4 tirapazamine-related toxicity occurred (not including radiation-related toxicity), all chemotherapy was withheld until the toxicity had improved by at least two grade levels. Subsequent tirapazamine doses required a 25% dose reduction. Cisplatin dose modification and delay were permitted, in accordance with standard practice at the study site. Radiotherapy was not to be interrupted for chemotherapy-related toxicity, unless the treating physician deemed that delayed radiotherapy was in the patient's best interest. Omitted doses of radiation were to be made up by subsequent twice-daily treatment. If chemotherapy was delayed for more than 2 weeks, radiotherapy was to be completed without any additional chemotherapy.

Neck Surgery

Patients who achieved a complete response at the primary site but had a residual neck mass at 12 weeks were to proceed to a neck dissection. An exception was made for patients with regressing nodal masses that were not metabolically active on [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) scan; these patients were monitored closely, and neck dissection took place only if regression ceased or there was a residual mass at the 26-week assessment. Planned dissections were not permitted if

complete clinical and radiological response of neck nodes was achieved, regardless of initial nodal size.

Randomization and Stratification

Randomization charts, in which approximate balance within strata (institutions) was maintained by the adaptive biased coin method, were prepared before start of accrual and kept at the Trial Centre; patients were randomized (1:1) by telephoning the Trial Centre data manager. The treatment allocation was unknown to the patient until the registration had been accepted.

End Points

A patient was defined to have a complete response if a clinical/radiological complete response was achieved in the primary site and neck nodes within 26 weeks of completing treatment. Failure was defined as persistent disease in the primary site, progression of disease in the neck in patients not undergoing neck dissection, residual disease left behind following neck dissection (if done), locoregional relapse following complete response, or distant metastases.

Failure-free survival was measured from randomization to the date of first failure or death; time to locoregional failure was measured from randomization to the date of locoregional failure; and overall survival was measured from randomization to the date of death, of whatever cause. All three times were censored by the close-out date; time-to-locoregional failure was also censored by distant metastasis and death without preceding failure.

Sample Size

The original accrual target was 60 patients but the Trial Management Committee extended the target to 120 patients, before any efficacy analysis, to permit individual centers more experience with the two regimens, and to add failure-free survival as a major end point of the study. (It was determined that 120 patients would provide 80% power to detect a 22% difference [40% *v* 62%] in 2-year failure-free survival rates). This is the report of an interim analysis; the final analysis is planned for 2 years from the end of accrual.

Statistical Methods

Analyses of failure-free survival, time to locoregional failure, and overall survival are based on the intention-to-treat policy. Complete response rates were calculated as percentages of all randomized patients. The Fisher's exact test (two-sided) was used to test for a difference in complete response rates between the treatment arms.

September 1, 2002, was the close-out date used for the first 110 eligible patients randomized, and a later time, that of the 26-week assessment, for the last 11 patients randomized (in the order that all patients analyzed had been followed to at least this 26-week assessment). This close-out date was chosen for the analysis performed for the study's presentation at the 39th Annual Meeting of the American Society of Clinical Oncology (Chicago, IL, May 31 to June 3, 2003).

The Kaplan-Meier method was used to estimate time-to-event curves. Patterns of first failure were analyzed using a competing risks analysis for the events: locoregional failure only, distant failure only, simultaneous (within 1 month) locoregional and distant failure, and death without a preceding failure. Thus, all patients who died or whose chemotherapy regimens failed were associated with exactly one of these events, and the incidences of first failure by each of these types was calculated as a function of time.[16] Log-rank (exact) and Cox regression methods were used to analyze time-to-event data. The planned primary analysis of failure-free survival by treatment arm was an unadjusted analysis, however secondary analyses comparing arms after adjusting for prognostic factors were also done. The prognostic factors, and their coding, were chosen a priori to be the same as those to be used in the follow-on phase III trial, namely site, stage, hemoglobin group, and performance status. Low hemoglobin was defined as less than 135 g/L in men or less than 125 g/L in women. Exact log-rank tests over strata were performed as confirmatory analyses to the Cox regressions.

Worst grades of acute and late toxicities between the treatment arms were compared using the Cochran-Armitage test for linear trend. Two-sided tests are used throughout. No formal adjustment for multiple comparisons has been made.

RESULTS

Patient Characteristics

Between September 1998 and May 2002, 122 patients were randomized in this trial. One patient was ineligible due to a cardiomyopathy, which left 121 patients who were included in this analysis. The median potential follow-up time from start of treatment to the close-out date was 2.6 years (range, 0.4 to 4.0 years). No patients were lost to follow-up.

Baseline patient characteristics were well-balanced between the two arms (Tables 1 and 2). Patients had predominantly oropharyngeal primaries and had advanced disease with 83% and 79% having stage 4 disease and 47% and 45%

Table 1. Patient Characteristics

	% of Patients	
	TPZ/CIS (n = 63)	Chemoboost (n = 58)
Sex		
Male	79	91
Female	21	9
Age, years		
Median	58	55
Range	38-74	43-75
ECOG performance status		
0	56	57
1	41	38
2	3	5
Primary site		
Oral cavity	3	7
Oropharynx	73	67
Hypopharynx	14	17
Larynx	10	9
Stage		
III	17	21
IV	83	79

Abbreviations: TPZ/CIS, tirapazamine, cisplatin, and radiation; Chemoboost, cisplatin and infusional fluorouracil; ECOG, Eastern Cooperative Oncology Group.

Table 2. Tumor Stage Versus Node Stage

	% of Patients per Arm									
	T1		T2		T3		T4		Total	
Stage	TPZ/CIS	Chemoboost	TPZ/CIS	Chemoboost	TPZ/CIS	Chemoboost	TPZ/CIS	Chemoboost	TPZ/CIS	Chemoboost
N0	—	—	—	—	5	14	6	5	11	19
N1	—	—	3	3	10	3	3	9	16	15
N2	5	4	10	17	22	14	20	19	57	54
N3	5	2	8	2	3	5	2	3	18	12
Total	10	6	21	22	40	36	31	36		

Abbreviations: TPZ/CIS, tirapazamine, cisplatin, and radiation; Chemoboost, cisplatin and infusional fluorouracil.

having T4 and/or N3 disease in the TPZ/CIS and chemoboost arms, respectively.

Efficacy

The complete response rate at 26 weeks following completion of treatment without any neck dissection was 71% (95% CI, 59% to 82%) in the TPZ/CIS arm, and 66% (95% CI, 52% to 78%) in the chemoboost arm ($P = .43$). The complete response rate including patients who had no tumor found at neck dissection was 81% (95% CI, 69% to 90%) in the TPZ/CIS arm, and 72% (95% CI, 59% to 83%) in the chemoboost arm ($P = .29$). Patterns of first failure are shown in Table 3: the cumulative incidence of locoregional failure at 2 years in the TPZ/CIS arm (14%) is lower than that in the chemoboost arm (30%). Two patients on the TPZ/CIS arm had salvage surgery for persistent disease in the primary versus three patients that had salvage surgery on the chemoboost arm. Nine patients (14%) on the TPZ/CIS arm achieved a complete response at the primary site but required a neck dissection versus eight patients (14%) on the chemoboost arm.

Overall, 51 patients have died or failed chemotherapy: 20 locoregional failures, 17 distant failures, and five locoregional/distant failures, and nine deaths without previous failure, as first events. Forty-two patients had died by the close-out date. The 3-year failure-free survival rates were 55% (95% CI, 39% to 70%) in the TPZ/CIS arm and 44% (95% CI, 30% to 60%) in the chemoboost arm (log-rank $P = .16$; hazard ratio = 0.65; 95% CI, 0.38 to 1.14; Fig 1). The 3-year locoregional failure-free rates (Kaplan-Meier) were 84% (95% CI, 71% to 92%) in the TPZ/CIS arm and 66% (95% CI, 51% to 79%) in the chemoboost arm (log-rank $P = .069$; hazard ratio = 0.46; 95% CI, 0.20 to 1.04; Fig 2). The 3-year overall survival rates were 60% (95% CI, 44% to 74%) in the TPZ/CIS arm and 46% (95% CI, 30% to 63%) in the chemoboost arm (log-rank $P = .28$; hazard ratio = 0.70; 95% CI, 0.38 to 1.28; Fig 3).

Cox regression analysis of failure-free survival, comparing treatment arms adjusting for prognostic factors, gave a borderline statistically significant result: TPZ/CIS:chemoboost hazard ratio of 0.57 (95% CI, 0.33 to 1.00; $P = .051$; Table 4). This result was supported by a stratified exact log-rank analysis, producing an estimated hazard ratio of 0.53 ($P = .014$). Similarly, Cox regression analysis of locoregional failure gave a statistically significant result: TPZ/CIS:chemoboost hazard ratio of 0.42 (95% CI, 0.18 to 0.95; $P = .038$). This result was supported by a stratified exact log-rank analysis (hazard ratio = 0.35; $P = .005$). The adjusted comparison

Table 3. Patterns of First Failure (competing risks analysis)

	% Cumulative Incidence at 2 Years			
Type of Failure	TPZ/CIS	SE	Chemoboost	SE
Locoregional (L + L/D)	14	5	30	7
Distant (D + L/D)	14	5	19	6
Death, no preceding failure	9	4	9	4
Any failure or death	37	7	49	8

Abbreviations: TPZ/CIS, tirapazamine, cisplatin, and radiation; Chemoboost, cisplatin and infusional fluorouracil; L, locoregional failure; D, distant failure; L/D, simultaneous (within 1 month) locoregional and distant failure.

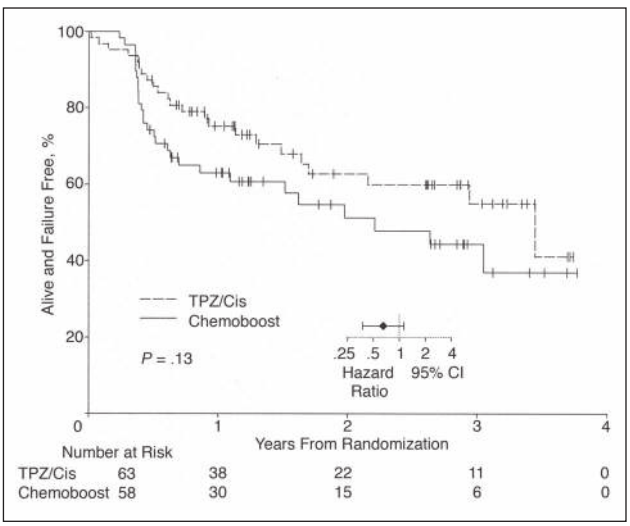

Fig 1. Failure-free survival by arm. Tick marks on the curves indicate censored times. TPZ/Cis, tirapazamine, cisplatin, and radiation; Chemoboost, cisplatin and infusional fluorouracil.

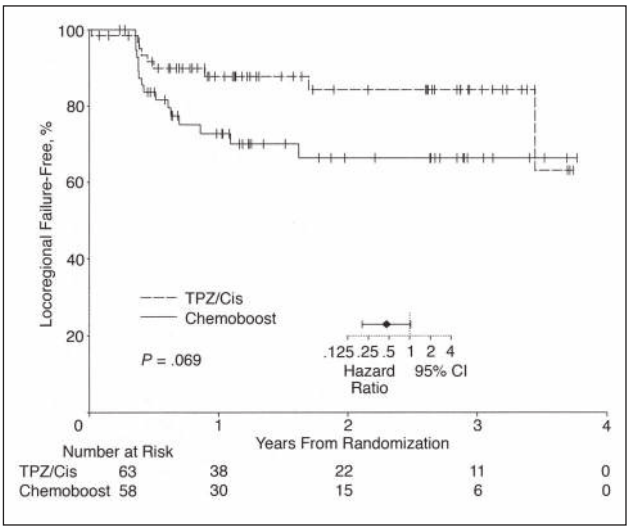

Fig 2. Time to locoregional failure by arm. Tick marks on the curves indicate censored times. TPZ/Cis, tirapazamine, cisplatin, and radiation; Chemoboost, cisplatin and infusional fluorouracil.

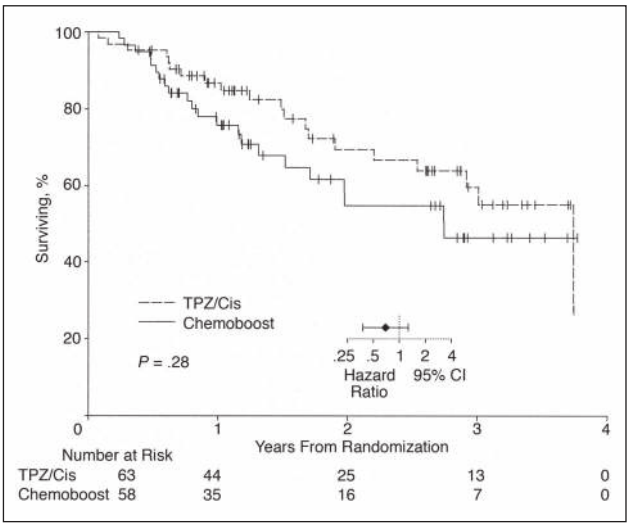

Fig 3. Overall survival by arm. Tick marks on the curves indicate censored times. TPZ/Cis, tirapazamine, cisplatin, and radiation; Chemoboost, cisplatin and infusional fluorouracil.

for overall survival was not statistically significant with a hazard ratio of 0.62 (95% CI, 0.33 to 1.15; $P = .13$) on Cox regression analysis, and 0.65 ($P = .15$) on the stratified log-rank analysis. Prognostic factor analyses of failure-free survival, locoregional control, and overall survival all revealed performance status (0:1, 2) to be a significant prognostic factor.

Acute Toxicity

Both regimens were associated with significant acute radiation toxicity (Table 5). There was no significant difference in the duration of acute mucositis (Fig 4A), but the acute skin reactions were more severe and protracted in the chemoboost arm, with a median duration of ≥ grade 2 skin reaction for 35 *v* 21 days in the TPZ/CIS arm ($P < .001$; Fig 4B). Seventy-five percent of patients on TPZ/CIS and 65% of patients on chemoboost received enteral feeding ($P = .22$).

Grade 3 and 4 neutropenia was more frequent in the TPZ/CIS arm than in the chemoboost arm (37% *v* 17%; $P = .001$; Table 6). Febrile neutropenia or grade 3 or 4 infection associated with grade 3 or 4 neutropenia occurred in 23% of patients in the TPZ/CIS arm (95% CI, 13% to 34%) versus 7.4% of patients in the chemoboost arm (95% CI, 2.6% to 17%; $P = .038$). There were five episodes of neutropenia associated with grade 3 or 4 chest infection, four in the TPZ/CIS arm, and one in the chemoboost arm. The median time to febrile neutropenia in the TPZ/CIS arm was 37 days (range, 29 to 54 days). One patient on TPZ/CIS who had pneumonia associated with neutropenia, appeared to be recovering from his pneumonia and was no longer neutropenic, but later developed recurrent pneumonia and died 50 days after starting radiotherapy. There were two other treatment-related deaths, one on each arm, both as a result of pneumonia not associated with neutropenia, occurring at 70 and 105 days after treatment began.

As expected, more nausea and vomiting was associated with the combination of tirapazamine and a higher dose of cisplatin than with the chemoboost regimen. Diarrhea, cramping, and skin rash are recognized toxicities of tirapazamine, and the incidence and severity of these toxicities in the TPZ/CIS arm were similar to previous trials. There was more fatigue ($P = .041$) and decline in performance status ($P = .02$) experienced during treatment by patients

Table 4. Multivariate Analysis of Failure-Free Survival Cox Regression Analysis of Treatment Arm, Adjusting for Four Prognostic Factors

Factor	Levels	Hazard Ratio	95% CI	*P*
Treatment arm	TPZ/CIS : Chemoboost	0.57	0.33 to 1.00	.051
Performance status	0 : 1, 2	0.30	0.16 to 0.56	< .001
Primary site	Oroph/larynx:Oral cav/hypoph	0.66	0.34 to 1.26	.21
Hemoglobin	High : low	0.95	0.51 to 1.78	.87
Stage	III : IV	1.18	0.55 to 2.54	.68

Abbreviations: TPZ/CIS, tirapazamine, cisplatin, and radiation; Chemoboost, cisplatin and infusional fluorouracil; Oroph, oropharynx; Oral cav, oral cavity; hypoph, hypopharynx.

Table 5. Acute Radiation Toxicity (EORTC-RTOG toxicity criteria)

	Grade	% of Patients per Arm: TPZ/CIS (n = 60)	Chemoboost (n = 57)	P
Mucositis	2	13	28	.080*
	3	80	72	
	4	5	0	
Skin	2	58	44	.012
	3	28	51	
Pharynx and esophagus	2	20	33	.89
	3	73	61	
	4	0	2	
Larynx	2	45	36	.51
	3	25	18	
	4	0	5	

NOTE. Four patients have been omitted from the analysis: three patients in the TPZ/CIS arm had less than 60 Gy and one patient in the chemoboost arm had no toxicity data.

Abbreviations: EORTC-RTOG, European Organisation for Research and Treatment of Cancer Radiation Therapy Oncology Group; TPZ/CIS, tirapazamine, cisplatin, and radiation; Chemoboost, cisplatin and infusional fluorouracil.

*P values for trend over all grades.

on the TPZ/CIS arm. There was no significant difference in weight loss between the two arms, with a loss of ≥ 15% of original weight compared to baseline occurring in 30% of patients in the TPZ/CIS arm and 37% of patients in the chemoboost arm.

Late Toxicity

There were four cases of grade 4 late mucous membrane toxicity in the tirapazamine arm, but no cases in the chemoboost arm. In one case, a pharyngolaryngectomy was performed for a radionecrotic ulcer; in another case, the patient died from distant metastases with a persistent ulcer in the base of the tongue that was biopsy negative; and in the two other cases the ulceration resolved. There were no significant differences in other late toxicities between the two arms (Table 7). Four patients (two on each arm) were reported to have grade 4 bone toxicity, which in three cases was temporary bone exposure that healed with conservative management. The fourth patient had osteoradionecrosis involving a 1-cm area of mandible that had not resolved at the time of the patient's death. There were four patients in the chemoboost arm who were documented to have late "grade 3" dysphagia, including two patients with esophageal strictures requiring dilation, but there were no documented cases in the TPZ/CIS arm. Although there was no difference in acute weight loss, at 12 months the mean weight loss in the TPZ/CIS arm was 9.6% (SE, 1.8%) versus 4.7% in the chemoboost arm (SE, 2.1%; $P < .001$). At 12 months, there were two patients on the tirapazamine arm and four patients on the chemoboost arm who were feeding-tube dependent. There were no significant differences in performance status between the arms at 3, 6, and 12 months. There were no grade 3 or worse late chemotherapy toxicities.

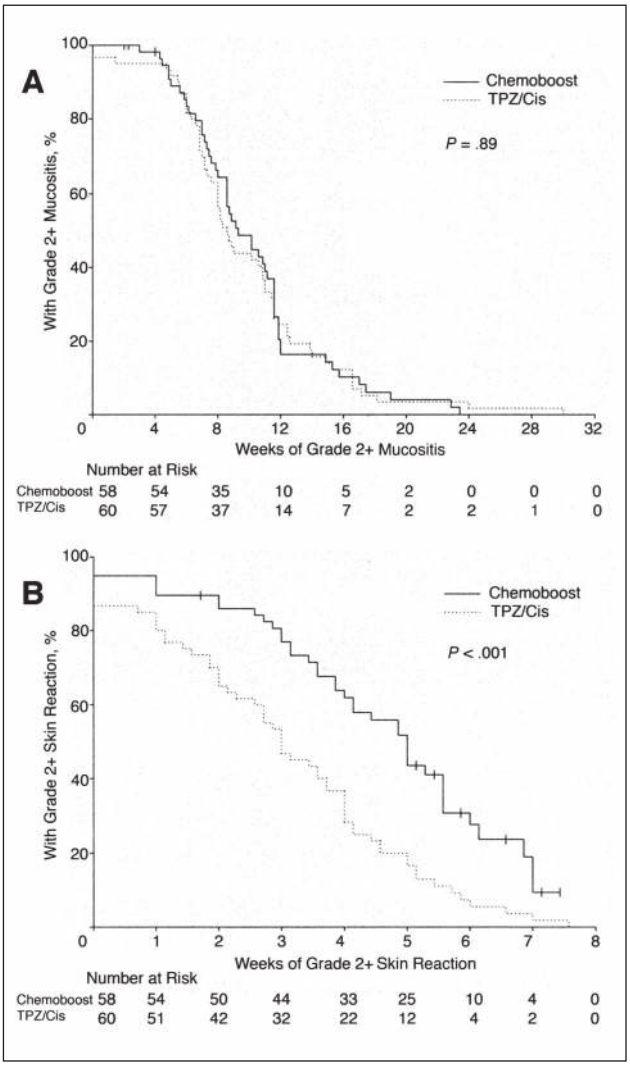

Fig 4. Duration of (A) acute mucositis and (B) acute skin reaction by arm (grade ≥ 2). TPZ/Cis, tirapazamine, cisplatin, and radiation; Chemoboost, cisplatin and infusional fluorouracil.

Treatment Delivery and Protocol Compliance

In the TPZ/CIS arm, 87% of patients received ≥ 66 Gy compared with 91% of patients in the chemoboost arm (Table 8). In both arms, 97% of patients who received at least 60 Gy completed treatment within 56 days. In the TPZ/CIS arm, 90% of patients received at least two of the three planned cisplatin doses, and 83% received at least eight of the nine planned tirapazamine doses (Table 8). The week-7 dose of chemotherapy was frequently omitted, with 57% of patients receiving all three cisplatin doses. In the chemoboost arm, 86% of patients received both planned cisplatin doses, and 81% received all 10 days of fluorouracil. Dose reductions were infrequent on both arms.

Table 6. Acute Toxicity (NCI-CTC, version 2.0)

	Grade	% of Patients per Arm: TPZ/CIS (n = 62)	Chemoboost (n = 54)	P
Neutrophils	2	28	17	.001*
	3	30	13	
	4	7	4	
Platelets	2	2	2	.038
	3	3	4	
	4	2	0	
Anemia	2	51	19	.008
	3	7	6	
	4	0	0	
Febrile neutropenia†	3	23	7	
Infection‡	2	5	11	
	3	5	6	
	4	5	2	
Nausea	2	29	28	.003
	3	13	4	
Vomiting	2	26	13	
	3	5	2	
Diarrhea	2	19	6	
	3	6	2	
Cramping	2	53	0	< .0001
	3	13	0	
	4	2	0	
Skin rash	2	11	0	< .0001
	3	5	0	
Fatigue	2	53	24	
	3	5	13	
Neuropathy	2	3	0	
	3	2	0	
Hearing	2	5	2	
	3	0	0	

NOTE. Five patients have been omitted from the analysis: one patient in the TPZ/CIS arm and four patients in the chemoboost arm received no chemotherapy. An additional patient in the TPZ/CIS arm had no hematologic toxicity data.

Abbreviations: NCI-CTC, National Cancer Institute Common Toxicity Criteria; TPZ/CIS, tirapazamine, cisplatin, and radiation; Chemoboost, cisplatin and infusional fluorouracil.

*P values for trend over all grades.

†Also includes patients with grade 3 or 4 infection with grade 3 or 4 neutropenia.

‡Not associated with neutropenia.

Table 7. Late Radiation Toxicity (EORTC-RTOG toxicity criteria)

	Grade	% of Patients per Arm: TPZ/CIS (n = 58)	Chemoboost (n = 55)
Skin	2	43	33
	3	0	2
Subcutaneous tissue	2	36	40
	3	12	4
Mucous membranes	2	60	55
	3	5	0
	4	7	0
Salivary glands	2	50	67
	3	36	27
Brain	2	2	2
Bone	2	2	2
	4	3	4

NOTE. Percent of patients/arm > grade 2 for toxicities occurring > 90 days after starting radiation, or after resolution of acute mucositis in the case of mucous membranes. Eight patients (five in the TPZ/CIS arm and three in the chemoboost arm) have been omitted from the analysis because < 60 Gy was given or early death meant there was no follow-up after 90 days.

Abbreviations: EORTC-RTOG, European Organisation for Research and Treatment of Cancer Radiation Therapy Oncology Group; TPZ/CIS, tirapazamine, cisplatin, and radiation; Chemoboost, cisplatin and infusional fluorouracil.

DISCUSSION

In this randomized phase II trial, we have demonstrated that both regimens are feasible, have acceptable toxicity profiles, and have promising efficacy in the cooperative group setting. In particular, the results of this trial confirm the promising efficacy observed in the phase I trial of tirapazamine, cisplatin, and radiation.[15] There is a trend in favor of the tirapazamine arm for both locoregional control and failure-free survival. After adjustment for known prognostic factors, the differences between the two arms become statistically significant for locoregional control and of borderline significance for failure-free survival.

When evaluating the promising efficacy of the TPZ/CIS regimen, the efficacy of the chemoboost regimen, compared with other platinum-based concurrent chemoradiotherapy regimens, needs to be considered. The chemoboost regimen has not been studied in phase III randomized trials to establish whether it has equal efficacy to other platinum-based–chemoradiotherapy regimens. An RTOG-randomized phase II trial evaluated chemoboost, a hydroxyurea/fluorouracil on alternate weeks regimen, and weekly cisplatin and paclitaxel.[17] In a preliminary report of this trial, there were no statistically significant differences between the three regimens, although the 2-year survival rate was 60% on the chemoboost arm versus 65% and 67% on the other two arms. All three regimens were claimed to be superior to cisplatin alone in a historical comparison to the results of the RTOG 8117 trial. While the historical comparison must be interpreted with caution, the RTOG results suggest that the chemoboost regimen has at least similar efficacy to other platinum-based–chemoradiotherapy regimens. The results with the chemoboost regimen in the TROG 98.02 trial are consistent with the results achieved in previous trials with this regimen,[10,11] and the results reported with other concurrent platinum-based chemotherapy and radiation combinations.[2,3,5]

Pinto et al[18] have reported the preliminary results of a single institution randomized trial of chemoradiotherapy with and without tirapazamine in patients with resectable stage 4 head and neck cancer. Patients were treated with induction chemotherapy (cisplatin and fluorouracil with or

Table 8. Treatment Delivery

	% of Patients per Arm	
	TPZ/CIS	Chemoboost
Radiotherapy dose*		
≥ 66 Gy	87	91
60-< 66 Gy	8	9
< 60 Gy	5†	0
Duration of radiotherapy‡		
≤ 49 days	73	86
50-56 days	24	11
> 56 days	3	4
No. of cisplatin doses		
3	57	—
2	33	86
1	8	7
0	2	7§
No. of tirapazamine doses		
9	54	—
8	29	—
7	8	—
6	3	—
< 6	6	—
Duration of FU infusion, days		
10	—	81
9	—	3
5-8	—	7§
1-4	—	2§
0	—	7‖

Abbreviations: TPZ/CIS, tirapazamine, cisplatin, and radiation; Chemoboost, cisplatin and infusional fluorouracil (FU).
*Minimum dose given to all sites with macroscopic disease.
†One patient stopped at 32 Gy due to poor compliance, one patient withdrew consent after 6 Gy, and one patient died before starting treatment.
‡For 115 patients who received ≥ 66 Gy.
§Doses omitted because of infection in 3 patients, and because of patient refusal in two patients.
‖Three patients deemed to be too unwell to receive chemotherapy, and one patient refusal.

without tirapazamine) followed by 66 to 72 Gy radiation with concurrent cisplatin and fluorouracil with or without tirapazamine in weeks 1 and 5. The tirapazamine dose during radiation was 160 to 260 mg/m^2 daily for 3 days with each chemotherapy cycle. Sixty-two patients were accrued over 5 years. No significant differences in organ preservation, locoregional control, disease-free survival, or overall survival were observed. While the small sample size limits any interpretation of the efficacy results, it should be noted that there are significant differences between this trial and the TROG 98.02 trial in the patient populations and the regimens studied. The promising results seen with the TROG regimen may relate to the possible importance of more frequent administration of tirapazamine during radiation, and more intensive treatment of the hypoxic component of the tumor during the early phase of radiation.

Similar to other concurrent chemoradiotherapy regimens, both the TPZ/CIS and chemoboost regimens were associated with significant but manageable toxicity. The acute skin reactions were more severe and of longer duration in the chemoboost arm, which can be attributed to the fluorouracil. There was more grade 3 and 4 late mucous membrane toxicity in the TPZ/CIS arm. Increased rates of late mucous membrane toxicity have been reported in other trials of more intensive chemoradiotherapy regimens.[19]

Not surprisingly, in view of the higher dose of cisplatin and the addition of tirapazamine, TPZ/CIS is associated with increased chemotherapy-related toxicity, most notably febrile neutropenia. Febrile neutropenia was the dose-limiting toxicity of this regimen in the phase I trial.[15] Neutropenia occurs predominantly in weeks 5 and 6, which coincides with the peak skin and mucositis reactions, providing a portal of entry as well as being a time at which patients are at risk of aspiration. We have not used prophylactic G-CSF because of concerns about the possible adverse effect of G-CSF on outcome in patients receiving G-CSF during radical radiation for head and neck cancer based on the results of the trial reported by Staar et al.[20] Considering the risks of aspiration pneumonia and febrile neutropenia, treating clinicians must be careful with patient selection, have appropriate facilities to manage the complications of chemoradiotherapy, and must monitor patients closely with a low threshold for commencing intravenous antibiotics.

The chemoboost regimen, with all the chemotherapy given over a 2-week period, is a less intensive regimen than TPZ/CIS. Although TPZ/CIS was associated with more fatigue and decline in performance status, it may not be any different in this respect from other higher-dose platinum regimens, eg, the widely used cisplatin 100 mg/m^2 in weeks 1, 4, and 7. In this multicenter trial, compliance with radiotherapy and chemotherapy was good. Similar to other platinum-based concurrent chemoradiotherapy regimens, week 7 chemotherapy was frequently omitted.[4,21,22]

Practice around the world differs regarding management of the neck following chemoradiotherapy. Although it is possible that different post-treatment neck dissection policies may influence treatment outcome, there are currently no data from randomized studies addressing this particular issue. There is a significant body of literature that demonstrates excellent regional control, without a post-treatment neck dissection, in patients who obtain a clinical and radiological complete response to nonsurgical treatment. In this trial, a policy that reserved neck dissection for patients with residual neck masses resulted in high rates of locoregional control in both arms. Furthermore, each center adhered to a consistent policy on neck management so that there was no bias in favor of one arm or the other.

Based on the results of the TROG 98.02 trial, a phase III trial comparing the TPZ/CIS to conventionally fractionated radiotherapy combined with cisplatin 100 mg/m^2 in weeks 1, 4, and 7 was designed, and is currently accruing patients. The cisplatin and radiation regimen was chosen because it is an accepted standard based on the results of randomized

trials.[4,6] Although the cisplatin doses differ in the two arms, the trial design will permit an accurate determination of the contribution of tirapazamine when added to chemoradiotherapy for patients with locally advanced head and neck cancer.

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Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant within the last two years: Danny Rischin, Sanofi-Synthelabo; Lester Peters, Sanofi-Synthelabo. Received more than $2,000 a year from a company for either of the last two years: Danny Rischin, Sanofi-Synthelabo.

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