Minocycline Reduces Chemoradiation-Related Symptom Burden in Patients with Non–small Cell Lung Cancer: A Phase II Randomized Trial

Xin Shelley Wang, MD, MPH[1], **Qiuling Shi, MD, PhD**[1], **Tito Mendoza, PhD**[1], **Steven Lin, MD, PhD**[2], **Joe Y. Chang, MD, PhD**[2], **Raza H. Bokhari, BA**[1], **Hui-Kai Lin, MS**[1], **Araceli Garcia-Gonzalez, MD, PhD**[1], **Mona Kamal, MD, PhD**[1], **Charles S. Cleeland, PhD**[1], **Zhongxing Liao, MD**[2]

[1]Department of Symptom Research, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

[2]Division of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Abstract

Purpose: In patients with non–small cell lung cancer (NSCLC), concurrent chemoradiation therapy (CRT) exacerbates a cluster of difficult-to-manage symptoms, especially cancer-related fatigue. Minocycline is a readily available, low-cost antibiotic with anti-inflammatory properties. We conducted a phase II randomized, double-blinded, placebo-controlled trial to investigate the effect of minocycline in reducing CRT-symptom burden in NSCLC.

Methods and Materials: Patients with NSCLC scheduled to receive CRT provided consent and were randomized to receive either minocycline (100 mg twice daily) or a matching placebo during 6 to 7 weeks of CRT. Patient-reported fatigue and other symptoms were assessed on MD Anderson Symptom Inventory weekly from the start of CRT for 12 weeks. The primary outcome was 12-week (±2 days) area under the curve (AUC) for symptom burden, which was compared between treatment groups.

Results: Forty of 49 enrolled patients (80%) were evaluable (19 on minocycline and 21 on placebo). There were no grade 3+ adverse events related to the study medication. Fatigue was significantly reduced in the minocycline group compared to placebo group during the 12-weeks trial period (AUC=31.2±14.2 vs. 45.0±20.9, P=0.011), with a large effect size (Cohen's *d*=0.77).

Correspondence and reprint requests: Xin Shelley Wang, MD, MPH, Professor, Department of Symptom Research, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1450, Houston, TX 77030, Phone: 713-745-3504; fax: 713-745-3475; xswang@mdanderson.org.

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Pain (Cohen's d=0.54) and shortness of breath (Cohen's d=0.55) were also significantly reduced in the minocycline group (all P<0.05).

Conclusion: Minocycline during CRT for NSCLC was feasible, had a low toxicity profile, and yielded a clinically and statistically significant positive signal in reducing symptom burden related to NSCLC and CRT. This study is a proof of concept so a larger trial in CRT patients is warranted.

INTRODUCTION

Concurrent chemoradiation therapy (CRT), a standard treatment option for patients with locally advanced non–small cell lung cancer (NSCLC)(1), is often associated with acute side effects from the radiation and chemotherapy including both systemic symptoms (eg, fatigue, sadness, distress, disturbed sleep, drowsiness, and lack of appetite) and localized symptoms from lung cancer and radiation-induced toxic effects such as pneumonitis or esophagitis (eg, coughing, shortness of breath, sore throat, and pain)(2,3). Previous symptom research in patients with NSCLC, undergoing CRT, demonstrated that high severity of symptom burden contributes to the patient's general distress during the course of treatment; fatigue is the most severe of these symptoms and is difficult to manage (4,5). The severity of CRT-related symptom burden is associated with an increased pro-inflammatory response (6,7). Our research goal has been to identify a new strategy for effective intervention against and/or prevention of the inflammation-driven fatigue symptom burden due to disease and aggressive therapy(8). Reduction of symptom burden impacts patient's functional status and facilitates compilation of curative therapies.

Minocycline, a broad-spectrum tetracycline-antibiotics has the ability to cross the blood brain barrier and reduce anxiety-like behaviors through modulating neuroinflammation in preclinical studies (9,10). Minocycline prevents hyperoxia-induced brain changes, modulate inflammatory signaling pathways and inhibited hypoxia-induced cytokine release (11-13). The therapeutic effects of minocycline have been investigated in a number of diseases where inflammation plays a critical role (10). Minocycline had long-lasting effects in preventing neuropathic pain (14) and was safe and effective for patients with rheumatoid arthritis in a 48-week double-blind placebo-controlled trial (15). It is now widely used in the management of dermatitis associated with targeted therapy in cancer (16)(17); use of prophylactic oral minocycline significantly reduced grade 2 rash compared to use reactive topical steroids (44.0% vs. 84.6%, p=0.04) (18) and reduced moderate/severe itching compared to placebo (20% v 50%, P = .05) (19) in colorectal patients and it's prophylactic use resulted in lower incidence of rash in pancreatic cancer compared to deferred treatment (47.7 vs. 80.8%, p<0.001) (20). Our preliminary studies and the published data by others showed that minocycline is safe with positive trend toward reducing the adverse events after cancer treatment (feeding tube, fatigue, diarrhea and neuropathy) (21-24). Those studies were either single arm Phase II or Phase III with small sample size and unpowered to detect the effect size or to show statistically significance reduction in the treatment-related toxicities in cancer patients after minocycline. To provide a proof of concept, we investigated minocycline's ability to reduce treatment-related symptoms during CRT in a phase II randomized, double-blinded, placebo-controlled clinical trial in patients with NSCLC.

METHODS AND MATERIALS

Participants

Eligible patients for this single institution, prospective, blinded, and placebo-controlled randomized trial were adults with NSCLC who following multidisciplinary evaluation had been dispositioned to receive CRT in in the Division of Radiation Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas. Patients were approached and offered enrollment in the study. Eligible patients were at least 18 years old, had a pathologic diagnosis of primary or recurrent NSCLC, had adequate renal and hepatic function, had to have good performance status (Eastern Cooperative Oncology Group Performance Status 0-1), could read and understand English, were scheduled for CRT, and provided study-specific written informed consent. Patients were enrolled prior to therapy under a protocol approved by the Institutional Review Board. The chemotherapy regimen (standard platinum/taxane-based doublets) was consistent for all patients and radiation modality was intensity modulated radiation (IMRT). Data on patients' characteristics, cancer therapy, comorbidities, and current medications were collected by research staff.

Randomization and Intervention

Prior to accruing the first patient, a randomization list for the entire sample was generated by the biostatistician stating into which group a patient will be randomized. This list containing the accrual number and treatment group information was set up in the Department of Biostatistics Clinical Trial Conduct website. Participants were randomized equally using a permuted block design pre-CRT to receive either minocycline (100 mg twice daily enterally) or matching placebo during the CRT course. The 6- to 7-week intervention period was chosen to align with the standard CRT period (from day 1 to the final day of the 6- to 7-week course of CRT). In this double blind study, patients, treating physicians and clinical research coordinators were unaware which intervention the patients received. The minocycline and placebo capsules were of identical size, color and shape.

The trial is registered at ClinicalTrials.gov: .

Patient-Reported Outcomes Tool: The MD Anderson Symptom Inventory–Lung Cancer

The MDASI is a patient-reported outcome (PRO) assessment tool validated for use in the cancer population(25). The severity of 13 common cancer-related symptoms during the previous 24 hours is assessed on a 0-10 numerical scale, with 0 being "not present" and 10 being "as bad as you can imagine." Three lung cancer module items were also used in this study (MDASI–Lung Cancer)(26). The MDASI—Lung Cancer also contains six items that describe the extent to which symptoms have interfered with various aspects of the patient's life during the past 24 hours, with 0 being "no interference" and 10 being "interfered completely." The MDASI–Lung Cancer was administered before the start of CRT (baseline) and then weekly during and after therapy for up to 12 weeks from the start of therapy.

The quality of life (QoL) scores were reported by the patients, using single item QoL and EuroQol 5-dimensional questionnaire (EQ-5D).

Other Assessments

Both study medication–related and CRT–related adverse events were prospectively assessed weekly by the study team and treating physicians during the CRT period and graded weekly according to Common Terminology Criteria for Adverse Events version 3. The treating physicians determined the severity of other observed adverse events and attributed them to study medication or to CRT. Safety and futility monitoring was overseen by our institutional Data Safety and Monitoring Board.

Statistical Analysis

The primary endpoint was the 12-week (±2 days) area under the curve (AUC), which used trapezoidal approximation of five pre-specified patient-reported symptoms (pain, fatigue, sleep disturbance, lack of appetite, and sore throat) as assessed by the MDASI–Lung Cancer during the trial. These symptoms were selected a priori as a representative combination of known to contribute significantly to symptom burden based on a previous study (6). As the goal of this study was to detect the potential signal from the benefit of minocycline to inform future clinical trial design, we decided to detect a relatively large standardized effect size (ES) of 0.80 (one-sided, 5% significance level) with 80% for the primary endpoint, requiring 20 evaluable patients per arm. T-test was used to assess the statistical significance of differences between the minocycline and placebo groups in AUCs of the five pre-specified symptoms, the five most severe symptoms observed and each of the symptoms from the clusters taken individually. We pre-specified that evaluable patients would have at least 2 weeks of symptom intervention and data and that patients with less would be replaced. The QoL scores over time were compared between the two study groups, using Wilcoxon test. The Fisher's exact Test (p-value) was used to compare the proportions of the Study Medication Satisfaction Scale between treatment arms. Forty-six percent of the patients indicated that they would be willing to use the symptom study medications if getting CRT again and 100% would recommend the symptom study medications to another patient undergoing CRT. Seventy-four percent of the patients reported that it was very easy taking the symptoms study medications in the form in which they were given and 66.67% rated their satisfaction with the symptom study medications as "very stratified".

Patients' clinical characteristics according to treatment group were compared using independent t-tests for continuous variables and chi-square tests for categorical variables. Aggregated adverse events were tabulated according to attribution and grade. Finally, to assess the impact of minocycline on symptoms over time, mixed-effects models were applied including a group by time interaction term. Baseline symptom score, age, race/ethnicity, education level, comorbid conditions, cancer stage, and previous treatment were included in the mixed-effects models. SAS 9.4 (Gary, NC).

RESULTS

Patient Characteristics

Table 1 presents the participants' demographic and disease characteristics. The groups did not significantly differ in these characteristics except for the fact that the patients in

minocycline group were statistically significantly younger compared to placebo group (median (range) 63 (47-83) vs 68 (56-77), *P*= 0.037).

Attrition, Compliance, and Toxicity

From January 2013 through August 2015, 56 eligible patients were approached, and 49 were enrolled and randomized: 25 to minocycline and 24 to placebo. Early drop-out or refusal to proceed after enrollment occurred for several reasons: 2 cancellation of the patient's radiation or chemotherapy plan, 1 did not start the study drugs, 5 stopped the study drugs within 1 week, and 1 completed less than 2 MDASI assessments after treatment start. Thus, among the 49 patients enrolled, 40 (80%) were evaluable: 19 of those in the initial minocycline group and 21 of those in the initial placebo group. Medication compliance (90.5%) was adequate, and weekly PRO symptom assessments (489/520, 94% observations) were completed at a high rate. Supplementary Fig 1 presents the CONSORT diagram. There were no grade 3+ adverse events related to the study medication. Table 2 summarizes the observed adverse effects.

Group Differences in Symptom Outcomes

At baseline, fatigue severity did not significantly differ between the minocycline and placebo groups. The MDASI AUC component score for the pre-specified primary outcomes (pain, fatigue, disturbed sleep, lack of appetite, and sore throat) significantly differed between the minocycline and placebo groups (mean MDASI composite score ±SD; 17.45±9.08 vs. 24.56±15.45), with a medium effect size (P=0.044, ES=0.56). For the five most severe symptoms observed in the study, which were fatigue, coughing, shortness of breath, pain, and poor appetite, we also observed significant symptom reduction in the minocycline group compared with the placebo group (mean MDASI composite score ±SD; 22.51±11.23 vs. 32.01±17.77) (P=0.026, ES=0.64; Table 3).

Among individual symptom outcomes, the most impacted was fatigue (Table 3 and Figure 1); the fatigue reduction in the minocycline group compared with that in the placebo group had the largest effect size (31.18±14.2 vs. 44.98±20.9, Cohen's *d*=0.77, *P*=0.011). The minocycline group also showed significant reductions in shortness of breath (21.53±15.76 vs. 32.45±23.02, Cohen's *d*=0.55, *P*=0.029) and pain (17.13±12.40 vs. 26.64±21.56, Cohen's *d*=0.54, *P*=0.046). There was no significant difference in the MDASI interference items, although the minocycline group showed less symptom interference than did the placebo group, with a small effect size ((mean total MDASI interference score ±SD; 14.11±10.21 vs. 20.05±18.45), Cohen's *d*=0.40, *P*=0.211). A similar trend was observed in the lesser severity of poor appetite in the minocycline group compared with the placebo group (mean MDASI score ±SD; 17.16±15.76 vs. 27.31±24.95), Cohen's *d*=0.49, *P*=0.069). No difference between groups was found for the lung symptom items (coughing (mean MDASI score ±SD; 25.55±16.28 vs. 28.69±19.01), Cohen's *d*=0.18, *P*=0.353) and sore throat (mean MDASI score ±SD; 4.45±7.23 vs. 4.36±9.51), Cohen's d=−0.01, *P*=0.489)).

Longitudinal modeling of the entire sample revealed an expected significant increase in mean fatigue level from baseline during CRT (est=0.18, *P*=0.0002), a significant decrease in fatigue during weeks after completion of CRT (est=−0.38, P<0.0001), and a significantly

lower mean fatigue level over the 12 weeks during and after CRT in the minocycline group compared with the placebo group (est=−0.65, P=0.025). On mixed modeling, there was a significant reduction in fatigue in the minocycline group compared with the placebo group over time (P=0.007), justified with covariance (baseline fatigue, age, race/ethnicity, cancer stage, comorbidity, ECOG-PS, education level, prior cancer treatment, and time in weeks).

Patients on minocycline reported better health-related quality of life (QoL) at week 12, measured by EQ-5D index (Mean±SD 0.89±0.14 compared to 0.82±0.13, P= 0.011) and single item QoL (Mean±SD 8.14±1.46 compared to 6.73±1.58, P=0.040). Overall, the patients were satisfied with the study medications, Supplementary Table 1.

DISCUSSION

In this phase II randomized, placebo-controlled trial in patients with NSCLC undergoing curative CRT, we observed a significant reduction in multiple patient-reported symptoms in those treated with minocycline compared with a placebo during the 12-week trial period. Minocycline was well tolerated, and compliance was high for the study medication and weekly PRO symptom assessments. Our results are consistent with the recent report of a significant symptom reduction in patients with head and neck cancer undergoing CRT or radiation therapy in a randomized phase II trial of minocycline versus placebo (21). Therefore, our findings encourage further clinical study of minocycline for symptom management in patients with NSCLC undergoing standard CRT.

Although we pre-specified a cluster of five PROs as the primary outcome of the trial, we learned that the five most severe symptoms in this trial were slightly different; coughing and shortness of breath were more severe than poor appetite and sore throat and so were included in a separate model also compared between groups individually. Nevertheless, for both outcome groupings, the minocycline group showed improvement in symptom severity compared with the placebo group, with similar effect sizes (Table 3). The consistency of the intervention's beneficial effect on individual symptoms on MDASI items presents the underlines the strength of the effect of minocycline for managing the most troublesome CRT-induced symptom burden in this patient sample. Increased fatigue severity over time (Fig. 1) was driven by the accumulated dose of CRT, which is consistent with previous symptom research (3,4) ; however, this fatigue was significantly decreased in the treatment group compared with the placebo group in the weeks after CRT completion.

Mostly because of the difficulty of timing blood sample collection, the study was limited by a lack of a translational component to confirm the intervention's benefit for inflammatory mechanisms. CRT-related fatigue has been associated with the inflammatory response (27) ; therefore, the mechanism of minocycline-induced fatigue reduction should be further studied. The second limitation of the study is lack of understanding of radiation parameters (such as PTV) associated effect of symptom reduction from minocycline. Although the randomized study design supports the result of this trial, it could be better reviewed in the future trial in these patients undergoing CRT.

The reduction in fatigue was the largest effect in our trial compared with the ES for other single symptoms on MDASI (Table 3). This result is encouraging after long frustration regarding fatigue reduction in oncology care with limited available pharmaceutical options (28-30). Furthermore, this study also demonstrated benefit from minocycline in the cluster of the most severe symptoms, including pain, poor appetite, and shortness of breath, all with a medium ES.

Adequate data on the appropriate timing of using the minocycline in relation to the cancer treatment course and the short/long-term effects of using minocycline on cancer treatment efficacy/resistance are lacking. Nevertheless, minocycline found to have a synergistic cytotoxicity effect (31-33), and its prophylactic use concurrent with anti-EGFR monoclonal antibodies was not associated with significant influence on tumor response in a retrospective study (18), thus safety and efficacy studies before concurrent use of minocycline and cancer treatment are warranted.

Although there is a growing role for immunotherapy in the treatment of NSCLC, the safety and efficacy of using minocycline concurrently or shortly after immunotherapy in patients with NSCLC have not yet been investigated. Yet, the immunomodulatory effect of minocycline has been successfully used in the treatment of the adverse events of immunotherapy in non-cancer conditions (34), and treated psychosis that may be associated with immunotherapy (35). However, minocycline or its metabolites could interact with the immune system and (36) triggers severe autoimmune conditions (37), thus, cancer patients on minocycline should be carefully monitored (38), especially if they are receiving immunotherapy. Underlying genetics mechanism was also proposed as another explanation for the minocycline-induced autoimmune phenomena (39).

The current trial has been conducted in the pre-immunotherapy era. Nevertheless, the drug interaction between minocycline and novel immunotherapy agents should be examined before moving to Phase III clinical study. Considering that steroids could be used in patients with NSCLC to relieve the RT-induced pneumonitis or immunotherapy-induced adverse events, concurrent use of minocycline with steroids also has not been adequately monitored in cancer patients, yet, minocycline found to have a steroid sparing effect in non-cancer conditions (40).

CONCLUSION

Minocycline for the management of CRT-related symptoms is feasible and has a low toxicity profile at 100 mg twice a day. Using minocycline at this dose yields a positive signal of its ability to reduce fatigue with a large effect size and to reduce the burden of the most severe symptoms overall with a medium effect size both during and after CRT. The results warrant a phase III trial of minocycline for CRT-related symptom reduction in patients with NSCLC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.
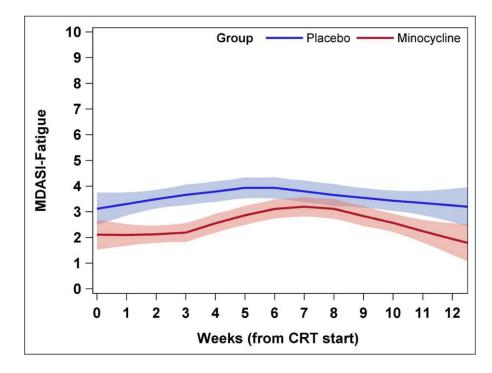
Acknowledgments

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Figure 1. Mean severity of fatigue by treatment group

Fatigue severity was measured on MD Anderson Symptom Inventory-Fatigue on 0-10 scale weekly during and after concurrent chemoradiation therapy. On longitudinal analysis, fatigue severity was significantly decreased in the minocycline group compared with the placebo group (est=−0.65, P=0.025), although fatigue significantly increased from baseline in both groups during the 7 weeks of chemoradiation therapy (est=0.18, P=0.0002) and decreased during weeks 7-12, after chemoradiation therapy (est=−0.38, P=0.025).

Table 1.

Patient characteristics

Continuous variables, mean (SD), median (range)		Minocycline (n=19)		Placebo (n=21)		P value
		Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)	
Age, years		62.4 (8.1)	63 (47-83)	67.3 (6.3)	68 (56-77)	0.037
Body mass index		33.0 (12.6)	28.3 (17.5-69.3)	29.2 (7.8)	28.7 (18.3-48.7)	0.261
Total radiation dose, Gy		62.9 (10.4)	66 (25-72)	62.5 (5.4)	66 (54-74)	0.229
Total fractions		32.7 (4.8)	33 (25-50)	32.6 (2.6)	33 (27-37)	0.895
Categorical variables, n, %						
Sex	Female	10	52.6%	10	47.6%	0.752
	Male	9	47.4%	11	52.4%	
Marriage	Married	17	89.5%	15	71.4%	0.154
	Unmarried	2	10.5%	6	28.6%	
Race/ethnicity	Non-Hispanic white	17	89.5%	19	90.5%	0.916
	Other	2	10.5%	2	9.5%	
Education	13 years or more	10	52.6%	11	52.4%	0.987
	0-12 years	9	47.4%	10	47.6%	
Cancer stage	I/II	3	15.8%	7	33.3%	0.201
	III/IV	16	84.2%	14	66.7%	
Charlson Comorbidity Index	0	10	52.6%	12	57.1%	0.775
	1 or more	9	47.4%	9	42.9%	
ECOG PS	0	11	57.9%	6	28.6%	0.061
	1	8	42.1%	15	71.4%	
Recurrent disease	No	18	94.7%	20	95.2%	0.942
	Yes	1	5.3%	1	4.8%	
Prior treatment	No	15	78.9%	13	61.9%	0.240
	Yes	4	21.1%	8	38.1%	
Prior radiation	No	19	100.0%	21	100.0%	
	Yes	0	0.0%	0	0.0%	
Prior chemotherapy	No	16	84.2%	14	66.7%	0.201
	Yes	3	15.8%	7	33.3%	
Prior surgery	No	17	89.5%	17	81.0%	0.451
	Yes	2	10.5%	4	19.0%	
Radiotherapy						0.115
	IMRT	16	84	13	62	
	Proton	3	16	8	38	

SD, standard deviation; ECOG PS, Eastern Oncology Group Performance Status

Table 2.

Toxicity by treatment group

		Attribution of AE to Study Medication						Total
		Possible		Unlikely*		Unrelated**		
		Minocycline	Placebo	Minocycline	Placebo	Minocycline	Placebo	
CTCAE grade, N[1]	1	0	0	1	2	1	5	9
	2	0	0	13	9	3	4	29
	3	0	0	3	2	2	5	12
	4	0	0	0	0	0	0	0
Total, N		0	0	17	13	6	14	50

[1]Number of events

*Grade 1 unlikely AEs include dermatitis, fever and weight loss.

*Grade 2 unlikely AEs include anorexia, dehydration, diarrhea, dysgeusia, dysphagia, dyspnea, erythema, esophagitis, esophagtis, fatigue, fever, and odynophagia

*Grade 3 unlikely AEs include cough, dehydration, dermatitis, dysphagia, and dyspnea.

**Grade 1 unrelated AEs include alopecia, dermatitis, erythema, high bilirubin, and odynophagia.

**Grade 2 unrelated AEs include AST increased, diarrhea, esophagitis, fatigue, odynophagia, rectal bleeding, and vomiting.

**Grade 3 unrelated AEs include dehydration, dysphagia, dyspnea, nausea, pain in extremity, and pulmonary embolism

CTCAE, Common Terminology Criteria for Adverse Events version 3

Table 3.

AUCs for symptom outcomes by treatment group

Outcome	Placebo (n=21)		Minocycline (n=19)		P value (one-sided t-test)	Cohen's d effect size
	Mean	SD	Mean	SD		
Pre-specified primary outcomes: fatigue, pain, disturbed sleep, poor appetite, sore throat	24.56	15.45	17.45	9.08	0.044	0.56
Five most severe adverse effects in the study: fatigue, coughing, shortness of breath, pain, poor appetite	32.01	17.77	22.51	11.23	0.026	0.64
Total interference	20.05	18.45	14.11	10.21	0.211	0.40
Fatigue	44.98	20.90	31.18	14.22	**0.011**	0.77
Pain	26.64	21.56	17.13	12.40	**0.046**	0.54
Disturbed sleep	19.50	16.41	17.34	14.29	0.331	0.14
Poor appetite	27.31	24.95	17.16	15.76	0.069	0.49
Shortness of breath	32.45	23.02	21.53	15.76	**0.029**	0.55
Sore throat	4.36	9.51	4.45	7.23	0.489	−0.01
Coughing	28.69	19.01	25.55	16.28	0.353	0.18
Drowsiness	24.17	19.09	20.61	14.83	0.224	0.21

AUC, area under the curve; SD, standard deviation. Numbers in bold indicate statistically significant P values.