Original Article

Phase 1 Dose-Finding Study of Metformin in Combination With Concurrent Cisplatin and Radiotherapy in Patients With Locally Advanced Head and Neck Squamous Cell Cancer

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BACKGROUND: The 5-year overall survival (OS) rate remains at 50% for patients with locally advanced head and neck squamous cell carcinoma (LAHNSCC), thereby underscoring the need for improved treatments. An antidiabetic agent, metformin, was found in retrospective studies to improve survival in patients with HNSCC. Therefore, the authors conducted a phase 1 dose escalation study combining metformin with chemoradiotherapy in patients with LAHNSCC. **METHODS:** Nondiabetic patients with LAHNSCC were enrolled in the current study to receive escalating doses of metformin and CRT based on the modified toxicity probability interval design. Metformin cohort doses included 2000 mg, 2550 mg, and 3000 mg daily in divided doses in addition to cisplatin (at a dose of 100 mg/m^2 on days 1, 22, and 43) and standard radiotherapy (70 grays). Adverse events were categorized as per the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). **RESULTS:** Twenty patients were enrolled, 2 of whom withdrew consent. The median age of the patients was 56 years and the majority were male (83%), were white (88%), had p16-positive disease (72%), and were tobacco users (61%). The median length of metformin exposure was 28.5 days. The most common grade ≥3 toxicities were nausea (11%), vomiting (11%), mucositis (6%), acute kidney injury (17%), anemia (6%), and leukopenia (11%). Dose-limiting toxicities included diarrhea and acute kidney injury. After a median follow-up of 19 months, the 2-year overall survival and progression-free survival rates were 90% and 84%, respectively. No hypoglycemia events or lactic acidosis were observed. Cisplatin administration did not appear to affect metformin pharmacokinetics. The maximum tolerated dose for metformin could not be determined given the limited number of patients who tolerated metformin during chemoradiotherapy. **CONCLUSIONS:** To the authors' knowledge, the current study is the first phase 1 trial combining metformin with chemoradiotherapy. Rates of overall survival and progression-free survival were encouraging in this limited patient population, and warrant further investigation in a phase 2 trial. ***Cancer* 2020;126:354-362**. © *2019 American Cancer Society*.

KEYWORDS: clinical trial, head and neck cancer, metformin, phase 1.

INTRODUCTION

According to the Surveillance, Epidemiology, and End Results (SEER) database, approximately 65,000 new cases of head and neck cancer are estimated to be diagnosed in the United States in 2019, with nearly 16,500 patient deaths expected this year.[1] Early-stage head and neck squamous cell carcinomas (HNSCCs) often are curable with single-modality treatment. However, approximately 60% of newly diagnosed patients present with locally advanced HNSCC (LAHNSCC) (American Joint Committee on Cancer eighth edition stage III or IV disease).[2] For patients who are unable to undergo surgery or who prefer organ preservation, available treatment options include concurrent chemotherapy and radiotherapy (CRT) or sequential induction chemotherapy followed by RT.[3] In a randomized phase 3 trial (Radiation Therapy Oncology Group [RTOG] 0522) comparing RT plus cisplatin with or without cetuximab for patients with stage III to IV HNSCC, the 2-year progression-free survival (PFS) rate was approximately 65% and the 2-year overall survival (OS) rate was approximately 80%.[4] Moreover, a previous meta-analysis of randomized controlled trials demonstrated that adding

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chemotherapy to RT does improve PFS and OS, but only with a 5-year survival rate of approximately 50%,[4,5] thereby underscoring the need for improved regimens.

Metformin (1,1-dimethylbiguanide hydrochloride) is an oral drug commonly used to treat patients with type 2 diabetes mellitus, polycystic ovary syndrome, and metabolic syndrome.[6] Animal models have proven metformin to work by inhibiting the mammalian target of rapamycin (mTOR) pathway along with an increase in the phosphorylation of 5' AMP-activated protein kinase (AMPK), leading to an antitumor effect.[7] Epidemiological studies that analyzed either all patients with head and neck cancer or those with laryngeal cancer have demonstrated that diabetic patients who are treated with metformin not only presented with earlier stage disease but had better outcomes when compared with diabetic patients who did not receive metformin.[8,9] Rego et al conducted a systematic review that demonstrated that metformin causes cell cycle arrest in the G_0/G_1 phase and apoptosis of cancer cells, thereby giving insight into possible mechanisms of metformin-mediated anticancer effects.[6] In addition, a "window of opportunity trial" in which metformin was administered to patients between the performance of biopsy and definitive surgical resection at a dose of 1000 mg twice daily demonstrated that metformin promoted apoptosis as well as increased stromal markers of metabolism (eg, caveolin-1 [*CAVI*] and B-galactosidase [*GALBG*]).[10] The impact of metformin on the metabolic milieu of the tumor microenvironment, especially its ability to reduce the level of hypoxia, is of special interest and has been explored in preclinical studies.[11,12] This metabolic effect of metformin also is believed to be the mechanism by which the sensitivity of tumor tissue to PD-1–blocking drugs increases, thereby laying the foundation for clinical trials combining metformin with immunotherapy drugs such as pembrolizumab.[13] In lung cancer cell lines, metformin also has been shown to be an effective radiosensitizer.[14] Given the anticancer properties of metformin due to its metabolic effects as well as its radiosensitization effects, we conducted a phase 1, open-label, single-site dose escalation study combining metformin with CRT in patients with LAHNSCC.

MATERIALS AND METHODS

Patients

Eligible patients were aged ≥18 years with histologically or cytologically confirmed, newly diagnosed, locally advanced stage III or stage IV HNSCC (T1-T2, N2a-N3, or T3-T4 according to the American Joint Committee on Cancer seventh edition) and an Eastern Cooperative Oncology Group performance status ≤1, and had adequate organ function. Exclusion criteria included patients with nasopharyngeal cancer, metastatic disease, or diabetes requiring insulin or receipt of metformin within the last 4 weeks; those with a history of other active intercurrent illnesses (eg, significant cardiovascular disease, viral infections, or major psychiatric illness); and patients receiving medications with the potential to induce lactic acidosis.

Study Design and Treatment

The current study was a single-center, open-label, nonrandomized phase 1 dose escalation trial of metformin in combination with CRT in previously untreated patients with LAHNSCC. The clinical trial was registered on ClinicalTrials.gov (ClinicalTrials.gov identifier NCT02325401). The study was approved by the institutional review board at the University of Cincinnati and was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent was received from all participating patients prior to study enrollment.

Radiotherapy

All patients were treated with standard-of-care RT, which entailed 70 grays (Gy) to macroscopic disease with margin and a simultaneous integrated boost of 56 Gy to areas at risk of microscopic disease, all delivered in 35 fractions. An optional, intermediate-dose volume of 63 Gy was allowed based on physician discretion to entail areas believed to be at higher risk of disease recurrence. Because all patients were treated with RT in the same fashion, the RT is believed to have had no bearing on outcomes or metformin-related toxicity.

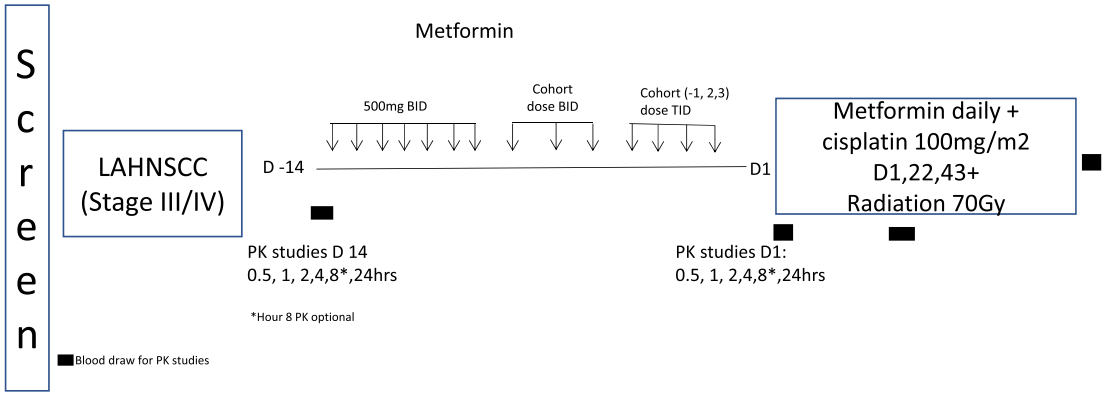
Chemotherapy

Patients were treated with institutional standard-of-care bolus cisplatin (100 mg/m^2 on days 1, 22, and 43) with intravenous hydration administered on the day of treatment and 2 days subsequently. Mannitol was added for those patients with central line access. Antiemetic premedications were used including a 5-HT3 antagonist, corticosteroids, and fosaprepitant. For acute nausea and vomiting, supportive care was given at the discretion of the treating investigator.

Metformin dose escalation phase

Cohorts of patients received escalating doses of metformin (2000 mg, 2550 mg, or 3000 mg divided into daily doses) with a 7-day to 14-day lead-in prior to CRT based on the modified toxicity probability interval design[15] (Fig. 1) to allow for possible re-escalation after previous de-escalation

A



B

Cohort	Metformin daily (in divided doses)
-1	1500 mg (500mg TID)
1	2000 mg (1000mg BID)
2	2550 mg (850mg TID)
3	3000 mg (1000mg TID)

C

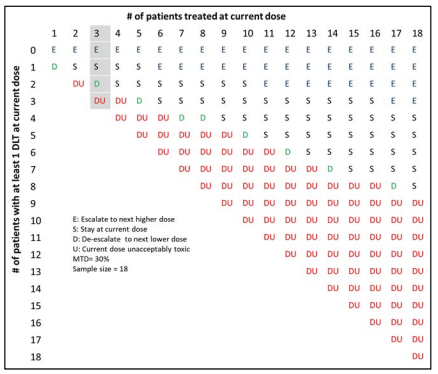


Figure 1. (A) Clinical trial schema. Eligible patients with locally advanced head and neck squamous cell carcinoma (LAHNSCC) (American Joint Committee on Cancer seventh edition stage III/IV) were consented to receive metformin during a lead-in period of 7 days (patients 1 to 7) or 14 days (from patient 8 onward). (B) The dose was escalated slowly to the allotted cohort dose over the lead-in period and then continued at the cohort dose during chemoradiotherapy. The starting dose of metformin was 2000 mg daily in divided doses in addition to cisplatin at a dose of 100 mg/m^2 on days (D) 1, 22, and 43 along with concurrent radiotherapy (2 grays [Gy] per day 5 days per week for a total of 70 Gy). A fall-back dose of 1000 mg daily (cohort 1) was included but not required during the study. Blood draws (indicated by black boxes) were performed on day -14, day 1, and subsequently while receiving treatment during week 3 and at the completion of treatment for pharmacodynamics. Pharmacokinetic (PK) blood draws were performed on day -14 and day 1 at 0, 0.5, 1, 2, 4, and 24 hours. Under the initial protocol, patients 1, 5, 6, and 7 were enrolled in cohort 1 and patients 2 to 4 were enrolled in cohort 2. Under the amendment, patients 8 and 9 were enrolled in cohort 1, patients 10 to 12 and 18 to 21 were enrolled in cohort 2, and patients 13 to 17 were enrolled in cohort 3. (C) Schematic for patient dose assignment based on modified toxicity probability interval design. The x-axis represents the total number of patients in each cohort and the y-axis represents the total number of patients with ≥1 dose-limiting toxicities (DLTs) recorded at that dose level. The shaded area represents the first 3 patients in the first cohort. "E" would result in escalation to the next cohort. "D" indicates de-escalation to the prior dose, "S" indicates that the next patient is to stay at the current dose, and "DU" indicates unacceptable toxicity and therefore no patients could be escalated back to this dose for the remainder of the study. However, the next patient could be de-escalated to the next lower dose until no further cohorts were available. The dose received by the majority of patients was confirmed to be the maximum tolerated dose (MTD). BID indicates twice daily; TID, 3 times a day.

and to maximize the ability to identify the maximum tolerated dose (MTD). Patients continued to receive metformin for the duration of CRT as tolerated. The study initially was designed to allow for a 7-day lead-in of metformin in which metformin was increased after 3 days to the full cohort dose, but, due to the occurrence of nausea with accelerated escalation to the full cohort dose, the study was amended (from patient 8 onward) to allow for a lead-in of 14 days and slower escalation to the cohort dose. During the lead-in period, patients were started on oral metformin at a dose of 500 mg twice daily on day -14 (day -7 for the initial amendment) (Fig. 1). They then were continued on this dose or were escalated to their final cohort dose of 3 times a day on day -3. The starting dose of metformin was 2000 mg daily in divided doses and the highest dose was 3000 mg daily. Metformin was taken with meals and withheld for 48 hours for any contrast scans. Patients were instructed to check their blood glucose on a daily basis. Metformin also was withheld for creatinine >1.5 mg/dL or a glomerular filtration rate (GFR) of <30 mL/minute.

Dose-limiting toxicity

The dose-limiting toxicity (DLT) was defined as the appearance of side effects during treatment that were severe enough to prevent further increases in the dose of metformin or to prevent the continuation of standard-of-care treatment at any dose level. DLTs were defined as metformin-related grade 3 or 4 nonhematologic toxicities other than alopecia, nausea, or vomiting, or those toxicities that the investigator determined were possibly, probably, or definitely related to metformin rather than standard-of-care treatment. Patients were considered evaluable for toxicity if they completed ≥3 doses of metformin. DLTs were assessed until 2 weeks after the completion of RT.

Three patients were enrolled into a cohort. The frequency of DLTs per cohort determined into which cohort the subsequent patients would be enrolled (Fig. 1). If no DLTs were identified, then up to 3 patients were enrolled at the next cohort level. However, if 2 total DLTs were experienced in any cohort level at any time during the process, the subsequent patients were to be enrolled into cohorts of 1 patient each until DLTs were assessed for all patients. The phase 1 portion was not considered complete until all 18 evaluable patients had been enrolled or the number of observed DLTs had resulted in an unacceptable dose at the lowest dose level.

Assessments

The primary endpoint of the current study was to determine the MTD of metformin in combination with CRT for patients with LAHNSCC. Key secondary endpoints included the evaluation of adverse events (AEs) (graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events [version 4.03]), the evaluation of PFS and OS at 2 years, and the effect of cisplatin pharmacokinetics (PKs) on the tolerability of metformin. Safety and tolerability assessments were conducted at the time of study visits, at the end of treatment, and during follow-up. After the completion of treatment, patients were followed monthly for the first 3 months and then every 3 months for the first year followed by every 6 months for 2 years for survival until death or withdrawal of consent. Patients were required to undergo positron emission tomography/computed tomography at 12 weeks to document treatment response.

Pharmacokinetics

For PK analysis, serial blood samples were collected at 0, 0.5, 1, 2, 4, and 24 hours after the administration of metformin on day -7 or day -14 and day 1. Metformin plasma levels were quantitated using a liquid chromatography–mass spectrometry method. The Thermo Fisher Scientific LTQ FT Ultra mass spectrometer, a hybrid mass spectrometer consisting of a linear ion trap and a Fourier-transform ion cyclotron resonance mass spectrometer, was used for the detection of metformin. Metformin was separated from other analytes by reverse phase chromatography using a Waters XBridge Amide column (2.1 mm × 100 mm, 3.5 μm). The composition of the mobile phase was 25:75 (95:5 water:acetonitrile 0.1% HCOOH; and 95:5 acetonitrile:water 0.1% HCOOH). Metformin and the deuterated internal standard metformin-d6 hydrochloride (Toronto Research Chemicals) were detected by multiple reaction monitoring of the 130.11 m/z → 60 m/z and 136.15 m/z → 60 m/z quantifying transitions for metformin and metformin-d6 hydrochloride, respectively. PK analysis was performed using noncompartmental analysis (Phoenix 64 WinNonlin; Certara USA Inc).

Correlative Pharmacodynamics

Blood samples were obtained for pharmacodynamics as shown in Figure 1. Samples were processed by a Clinical Laboratory Improvement Amendments (CLIA)–certified clinical laboratory for the determination of glucose, lactate levels (to document any signs of developing lactic acidosis), vitamin B12 (given that long-term use of metformin has been associated with low vitamin B12 levels),[16] and C-peptide levels (to study the impact on pancreatic β cells).[17]

TABLE 1. Baseline Patient and Disease Characteristics

Patient Characteristics	No. (%)	
Median age (range), y	56 (46-65)	
Sex		
Male	15 (83%)	
Female	3 (17%)	
Race		
White	16 (89%)	
African American	2 (11%)	
Tobacco abusers	11 (61%)	
p16 positive	13 (72%)	
Primary tumor site		
Oropharynx	12 (67%)	
Larynx	6 (33%)	
AJCC stage	AJCC 7	AJCC 8
I		4 (22%)
II		2 (11%)
III	2 (11%)	8 (44%)
IVA	12 (67%)	4 (22%)
IVB	4 (22%)	
Tumor classification		
T1 or T2	4 (22%)	6 (33%)
T3 or T4	12 (67%)	10 (56%)
Tx	2 (11%)	2 (11%)
Lymph node classification		
N0	2 (11%)	2 (11%)
N1	1 (6%)	5 (28%)
N2a or N2b	6 (33%)	5 (28%)
N2c	6 (33%)	3 (17%)
N3	3 (17%)	3 (17%)

Abbreviations: AJCC, American Joint Committee on Cancer; AJCC 7, American Joint Committee on Cancer seventh edition; AJCC 8, American Joint Committee on Cancer eighth edition.

TABLE 2. Summary of Treatment-Related Adverse Events[a]

Adverse Event	Any Grade No. (%)	Grade 1-2 No. (%)	Grade 3-4 No. (%)
Gastrointestinal			
Diarrhea	8 (44%)	7 (39%)	1 (6%)
Nausea	14 (77%)	12 (67%)	2 (11%)
Vomiting	9 (50%)	7 (39%)	2 (11%)
Reflux	5 (28%)	5 (28%)	0
Mucositis	5 (28%)	4 (22%)	1 (6%)
Other (abdominal pain, dysphagia, altered taste)	8 (44%)	8 (44%)	0
Metabolism and nutrition disorders			
AKI	8 (44%)	5 (28%)	3 (17%)
Lactic acidosis	0	0	0
Electrolyte abnormalities	4 (22%)	4 (22%)	0
Blood and lymphatic system disorders			
Leukopenia/neutropenia	5 (28%)	3 (17%)	2 (11%)
Anemia	5 (28%)	4 (22%)	1 (6%)
Investigations			
LFT abnormalities	2 (11%)	2 (11%)	0
Ear and labyrinth disorders			
Tinnitus, hearing loss, ear pain	4 (22%)	4 (22%)	0

Abbreviations: AKI, acute kidney injury; LFT, liver function test.
[a]Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).

Statistical Analyses

The dose-finding part of the study was to enroll a maximum of 18 evaluable patients. The sample size was chosen based on the maximum number of patients who could have been enrolled on a 3+3 design studying 3 doses. Secondary endpoints of safety as assessed by clinical review of AEs and laboratory tests were analyzed using appropriate summary statistics. Any patient who had received ≥3 days of treatment with metformin was considered evaluable for toxicity. Secondary efficacy endpoints (OS and PFS) were analyzed using Kaplan-Meier summary statistics. PFS was defined as the duration of time from the initiation of treatment to disease progression and OS was considered the duration of time a patient was alive from the initiation of treatment until the time of death. Comparisons of Kaplan-Meier survival data between different subgroups were conducted using the log-rank test. A P value <.05 indicated a statistically significant difference between the subgroups. For correlative pharmacodynamics analysis, patients' glucose, vitamin B12, and C-peptide levels were measured before administration of metformin, before chemotherapy, and off metformin. Measurements (before chemotherapy and off metformin) were compared with those from before metformin using 2-sample Student t tests for paired data. The data cutoff for these analyses was October 22, 2018. All statistical analyses were performed using R statistical software (version 3.3.3; R Foundation).

RESULTS

Patient Characteristics and Disposition

Between May 11, 2015, and December 26, 2017, a total of 21 patients were consented with 20 patients enrolled. Two patients withdrew consent during the metformin lead-in period due to non–DLT-related reasons. The remaining 18 patients were included for analysis. The median age of the cohort was 56 years (range, 46-65 years); the majority of the enrolled patients were male (83%) and white (88%). Approximately 61% of the patients were tobacco users (>10 pack-years). Thirteen patients tested positive for p16 expression (the remaining 5 patients either were negative or did not have p16 analysis completed) (Table 1). In approximately 50% of patients, metformin was discontinued or interrupted due to an AE; a total of 10 patients were able to remain on metformin during CRT for a sufficient period of time (less than one-half the duration of CRT).

Dose Escalation, DLTs, and MTD

Because of early nausea in the lead-in period, the protocol was amended after patient 7 to allow for the slower

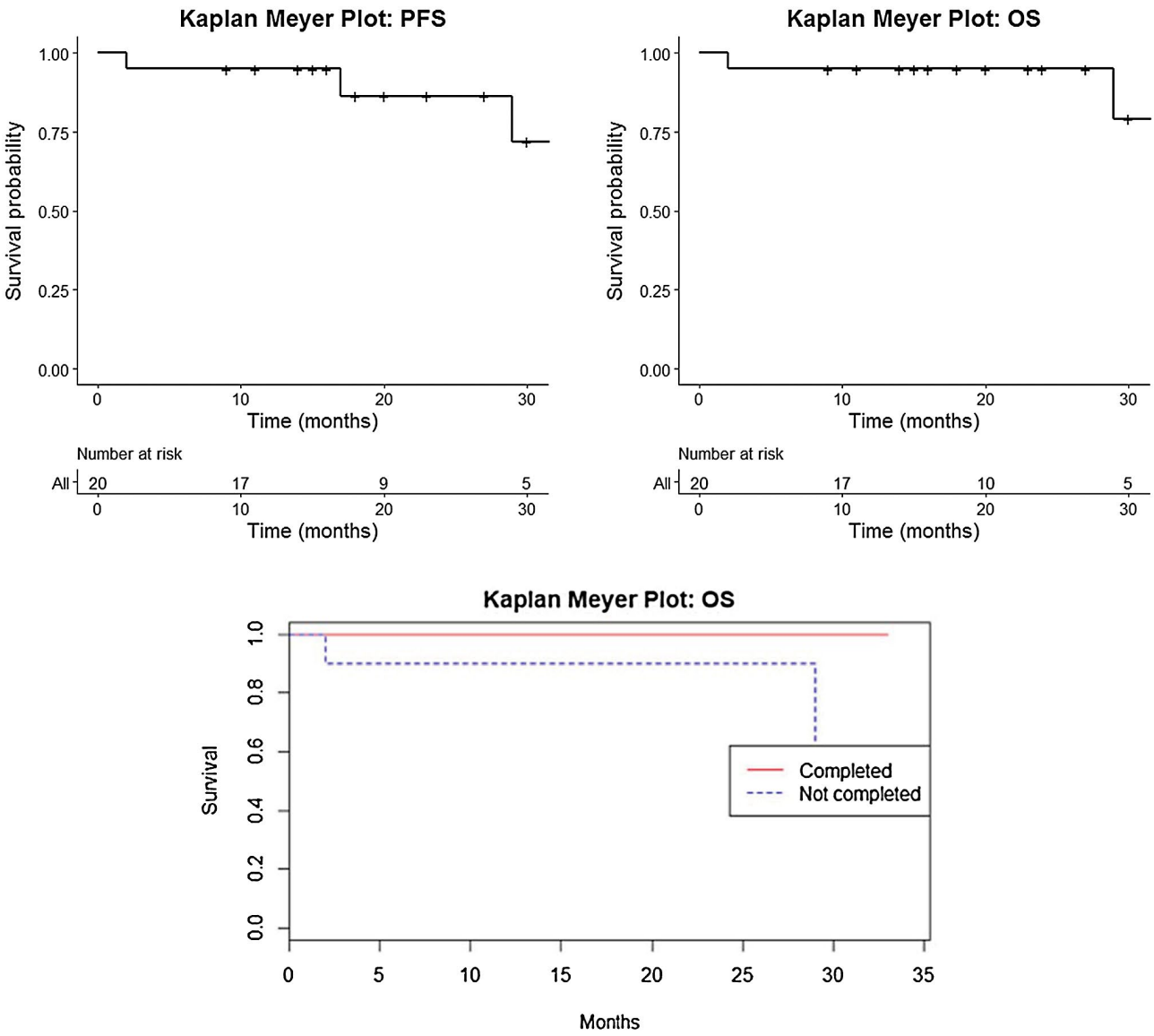


Figure 2. Kaplan-Meier curves of investigator-assessed (A) progression-free survival (PFS) and (B) overall survival (OS). Hash marks indicate censored observations.

escalation of metformin to the cohort dose. Of the evaluable patients, approximately 85% experienced ≥1 AEs (Table 2). The most common AEs were related to the gastrointestinal tract, with nausea observed in 77% of the patients followed by vomiting and diarrhea. DLTs included grade 3 diarrhea (cohort 3) and acute kidney injury (cohort 2), the latter of which occurred prior to the initiation of CRT. The most common grade ≥3 toxicities were diarrhea (6%), nausea (11%), vomiting (11%), mucositis (6%), acute kidney injury (17%), anemia (6%), and leukopenia (11%), the majority of which were related to standard-of-care treatment rather than metformin. Lactic acidosis was not observed. Based on the modified toxicity probability interval design, the MTD for metformin could not be determined reliably given the limited number of patients who tolerated the drug during CRT. However, a dose of 2550 mg daily in combination with CRT was found to be the highest dose tolerated at the highest frequency, suggesting that this dose may be acceptable as a recommended phase 2 dose.

Survival Outcomes

After a median follow-up of 19 months, the 1-year OS and PFS rates both were 90%. The 2-year OS and PFS

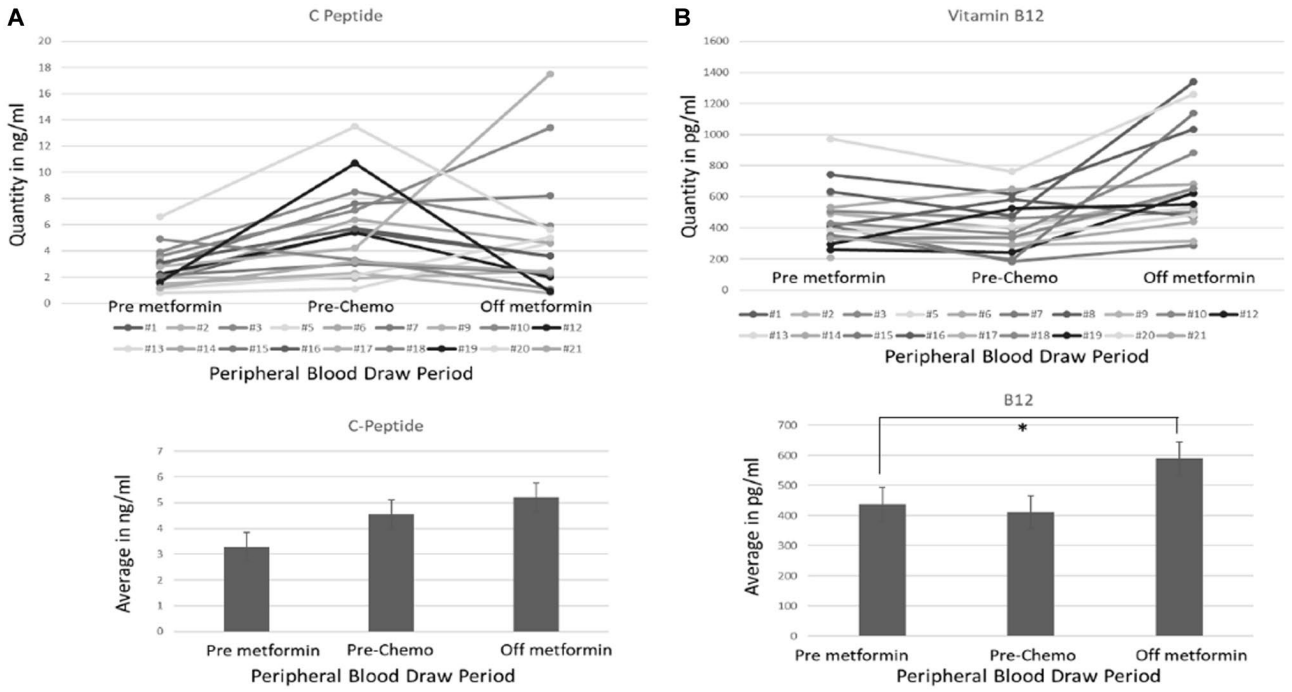


Figure 3. Metformin effects on laboratory blood levels. Levels of (A) C-peptide and (B) vitamin B12 before (pre) metformin, during metformin, and off metformin. Chemo indicates chemotherapy.

rates were 90% and 84%, respectively (Fig. 2). Two deaths were reported during the course of follow-up. One patient had a sudden unexplained death within 3 to 4 days of the completion of CRT; the patient had received only 5 days of metformin lead-in. The other patient died 29 months after the completion of treatment. Both deaths were deemed unrelated to metformin and unlikely related to disease. One patient experienced disease recurrence 17 months after the completion of CRT and underwent salvage surgical resection and subsequently was free of disease at the time of last follow-up.

Pharmacodynamics

Blood samples were collected prior to receipt of metformin (day -7 or day -14), after metformin lead-in but prior to CRT (day 1), and after the completion of therapy. Vitamin B12, glucose, C-peptide, and lactate levels were measured. No elevations in lactate that were concerning for lactic acidosis were observed. In addition, glucose levels did not decrease significantly during treatment with metformin. An increase in C-peptide was observed after metformin lead-in in the majority of patients that returned to baseline after treatment, but changes were not statistically significant (Fig. 3). It is important to note that vitamin B12 levels were decreased by metformin administration in the majority of patients and supplementation was required in one patient, although this finding was not statistically significant (Fig. 3). It is interesting to note that the vitamin B12 levels returned to above baseline after metformin treatment was completed ($P < .001$).

Archival tissue immunohistochemistry analysis revealed activation of the mTOR pathway, suggesting that these patients would benefit from mTOR pathway inhibitors such as metformin (see Supporting Fig. 1 and Supporting Table 1).

Pharmacokinetics

Metformin is excreted primarily unchanged by the kidney, with a mean renal clearance (CL_R) of 500 mL/minute. This indicates that the CL_R of metformin is higher than the GFR, and active tubular secretion is the principal mechanism of metformin elimination.[18] Cisplatin is well known to cause nephrotoxicity.[19] Approximately 50% of the cisplatin administered is excreted renally within the first 24 hours. As such, the concentration of platinum achieved in the renal cortex is several-fold greater than that in plasma and other organs.[20] Cisplatin primarily injures the S3 segment of the proximal tubule, causing a decrease in the GFR.[21] In fact, its adverse effect on kidney function is one of its primary DLTs. Thus, in the

current combination study, the systemic exposure (plasma levels and the overall area under the curve) of metformin may have been impacted considerably by the coadministration of cisplatin. The nephrotoxic effects of cisplatin potentially could reduce the metformin CL_R, resulting in an increase in the systemic exposure. Therefore, for those patients for whom sufficient blood samples were collected, we performed PK studies at multiple time points. It was observed that the area under the curve on day 1 did increase with escalation of the metformin dose, as would be expected (6181 ± 4340 ng/mL*hour in cohort 1 compared with 8499 ± 3032 ng/mL*hour in cohort 3) (Table 3). Although there was substantial patient intersubject variability, it is important to note that the creatinine clearance did not appear to affect acute concentrations of metformin in these patients. Longer term effects were unable to be analyzed in the current study.

DISCUSSION

In the current study, we have presented the results of a phase 1, dose-finding clinical trial of metformin added to CRT in patients with LAHNSCC. In previous retrospective studies and systematic reviews, metformin has been suggested to decrease not only the rates of locoregional disease recurrence but also the OS among patients with HNSCC.[22] Several studies have demonstrated the potential safety and efficacy of metformin in cancers other than HNSCC, including rectal cancer, acute lymphoblastic leukemia, and lung cancer.[23-26] Herein, we conducted what to our knowledge is the first phase 1 clinical trial to date to evaluate metformin combined with CRT in patients with LAHNSCC.

The MTD for metformin could not be established reliably from the current study given that only 10 of the 18 evaluable patients were able to tolerate metformin through a significant portion of CRT. However, 2550 mg daily was found to be the highest dose with the most tolerable profile in the current study, suggesting that it may be the most reliable dose for subsequent phase 2 studies. Given that DLTs were to be collected until 2 weeks after the completion of RT, this does limit the reliability of the full assessment of DLTs with the combination in the current study. Patients experienced DLTs at dose levels 2 and 3. Side effects predominantly involved the gastrointestinal tract and kidneys, and typically were related to dose. No deaths related to metformin were reported in the current trial. Overall, the combination was safe but with limited tolerability with CRT due to gastrointestinal toxicity.

The small number of patients included in the current study as well as its design limited our ability to

TABLE 3. Pharmacokinetic Assessments of Metformin Showing Parameters of Metformin for Various Dose Cohorts Computed Using Noncompartmental Analysis[a]

Dose Cohort	Dose, mg		T_{max}, Hours		C_{pmax}, ng/mL		AUC (0-4 Hours), ng/mL*Hour	
	Day -7 or Day -14	Day 1	Day -7 or Day -14	Day 1	Day -7 or Day -14	Day 1	Day -7 or Day -14	Day 1
1	500 bid	1000 bid	2.5 ± 1.2 (6 patients)	4 (2 patients)	1647 ± 551 (6 patients)	2045 ± 1022 (2 patients)	4828 ± 1469 (6 patients)	6181 ± 4340 (2 patients)
2	500 bid	850 tid	1.9 ± 0.9 (9 patients)	2.7 ± 1.2 (3 patients)	1139 ± 386 (9 patients)	2030 ± 550 (3 patients)	3572 ± 1323 (9 patients)	6354 ± 2050 (3 patients)
3	500 bid	1000 tid	2.4 ± 0.9 (5 patients)	2 (3 patients)	1215 ± 483 (5 patients)	2585 ± 1007 (3 patients)	3633 ± 1460 (5 patients)	8499 ± 3032 (3 patients)

Abbreviations: AUC, area under the curve, bid, twice daily; C_{pmax}, maximum (or peak) serum concentration; tid, three times a day; T_{max}, time at which the maximum (or peak) serum concentration is observed.
For analysis, serial blood samples were collected at 0, 0.5, 1, 2, 4, and 24 hours after the administration of metformin on day -7 or day -14 and day 1. Metformin plasma levels were quantitated using a Liquid chromatography–mass spectrometry method.
[a]Data are shown as the mean ± SD.

draw conclusions regarding the efficacy of metformin. Nevertheless, the 2-year OS and PFS rates of 90% and 85%, respectively, were found to improve when compared with historical control rates of 80% and 65%, respectively. However, this finding could be influenced by the high prevalence of p16 positivity in the patient population in the current study, which may have confounded the results. Metformin warrants further investigation in a phase 2 trial, but would be better tolerated in combination with less emetogenic systemic therapies.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Shuchi Gulati: Conceptualization, methodology, visualization, validation, writing–original draft, writing–review and editing, and funding acquisition. **Janki Desai**, **Sarah M. Palackdharry**, **John C. Morris**, **Muhammad K. Riaz**, **Vinita Takiar**, **Michelle Mierzwa**, **J. Silvio Gutkind**, **Alfredo Molinolo**, **Pankaj B. Desai**, and **Nooshin Hashemi Sadraei:** Formal analysis, project management, supervision, validation, and writing–review and editing. **Zheng Zhu** and **Roman Jandarov**: Formal statistical design and analysis and writing–review and editing. **Trisha M. Wise-Draper:** Conceptualization, methodology, supervision, visualization, validation, writing–review and editing, and funding acquisition.

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