Original Study

A Phase II Study of Capecitabine/Oxaliplatin With Concurrent Radiotherapy in Locally Advanced Squamous Cell Carcinoma of the Anal Canal

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Abstract

This was a single-arm phase II trial with locally advanced squamous cell carcinoma of the anal canal (SCCA) patients, to evaluate the feasibility of a more convenient therapeutic regimen composed of XELOX (capecitabine and oxaliplatin) concurrent with radiation therapy (XELOX-XRT). Complete response and Grade 3 toxicity rates occured in 19 patients (100%) and in 2 patients (22% of the group with adjusted dose), respectively. XELOX-XRT might be an alternative therapeutic regimen for SCCA patients.

Introduction: Squamous cell carcinoma of the anal canal (SCCA) presents a rising incidence in the United States. Standard of care for locally advanced disease is comprised of infusional 5-fluorouracil with mitomycin C or cisplatin concurrent with radiation therapy (RT). We designed this trial to evaluate the efficacy and safety of a more convenient regimen composed of capecitabine and oxaliplatin. **Patients and Methods:** This was a single-arm, phase II trial, with treatment-naive stage II to IIIB (TX,1-4NxM0) SCCA patients. The regimen was composed of capecitabine (825 mg/m^2 twice per day for 5 days) and oxaliplatin (50 mg/m^2 weekly) during weeks 1 through 6, concurrent with RT (XELOX-XRT; group 1). After the first 11 patients, the study was amended to omit chemotherapy during the third and sixth weeks (group 2). The primary objective was 3-year time to treatment failure (TTF) and safety. Secondary objectives were complete response (CR) rate, locoregional control, colostomy-free survival (CFS), and overall survival (OS). **Results:** Twenty patients were enrolled. Seven patients of group 1 (63%) developed Grade 3 toxicity, which reduced to 22% in Group 2. No Grade 4 toxicities were noted. The median RT dose was 55 Gy. CR occurred in 100% of the 19 patients evaluable for response at 12 to 14 weeks. After a median follow-up of 47.6 months, 2 patients had local recurrence and 1 had distant recurrence. Three-year TTF was 90.0%, with similar rates between groups 1 and 2 (respectively, 90.9% vs. 88.8%, $P = .984$). Three-year CFS was 90.0%. The median OS has not been reached. **Conclusion:** The XELOX-XRT regimen is safe, with promising efficacy, and should be explored in larger trials for the treatment of locally advanced SCCA.

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Keywords: Anal cancer, Combined modality therapy, Objective response, Radiation therapy, Time to treatment failure

Introduction

Squamous cell carcinoma of the anal canal (SCCA) is a malignancy comprising only 1.5% of all gastrointestinal malignancies.[1] Combined chemoradiation therapy is provided with curative intent for localized disease.[2-4] However, often considered rare in incidence, the incidence continues to rise annually in the United

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Table 1 Chemotherapy Regimen

Drug	Route	Dose	Schedule
Oxaliplatin	Central line, I.V.	50 mg/m^2	Days 1, 8, 22, and 29 during radiation therapy only
Capecitabine	Oral	825 mg/m^2, twice daily	Given Monday to Fridays only, on days of radiation therapy only. Weeks 1-2 and 4-5 only

States by 2.2% per year.[5,6] For the past 3 decades, previous pivotal trials have supported the use of 5-fluorouracil (5-FU) with mitomycin C (MMC) as a standard chemotherapy regimen with concurrent radiation therapy for curative intent.[2-4,7] 5-FU with cisplatin has also been investigated as an alternative regimen for radiation sensitization.[2-4] Regardless, each regimen requires intravenous administration, which can be tedious for some patients. Within the past decade, the oral fluoropyrimidine, capecitabine, has been determined to be an option for intravenous 5-FU for radiation sensitization and for systemic treatment in colorectal cancer.[8,9] In addition, the third-generation platinum agent, oxaliplatin, has also been determined to have similar properties.[10-12] Therefore, to explore this concept, a phase II trial of XELOX (capecitabine with oxaliplatin) with concurrent radiation therapy (XELOX-XRT) was conducted to explore the use of this combination in locally advanced SCCA.

Patients and Methods

Study Design and Participants

The present study was a single-arm, phase II trial, completed at M.D. Anderson Cancer Center. Patients were required to be treatment-naive. All patients were required to be stage II to IIIB according to the American Joint Committee on Cancer (TX, 1-4 NxM0); 16 years old or older, and Eastern Cooperative Oncology Group performance status 0 to 1. Patients were required to have a baseline computed tomography (CT) scan of the chest, abdomen, and pelvis but were not required to have measurable disease according to CT scan to be eligible. Palpable inguinal lymphadenopathy on baseline physical exam required an ultrasound-guided fine-needle aspiration for accuracy of staging and to ensure the radiation fields were accurate. All patients underwent baseline examination with anoscopy and rigid or flexible proctosigmoidoscopy before radiation therapy. Baseline laboratory value requirements for patients included absolute neutrophil count of $\geq$1500/μL, platelet counts $\geq$100,000/μL, total bilirubin $\leq$1.5 upper limit of normal (ULN), aspartate aminotransferase (AST)/alanine aminostransferase (ALT) $<$ 3 times the ULN, and creatinine of $\leq$1.5 mg/dL or creatinine clearance (CrCl) $\geq$ 50 cc per minute. Exclusion criteria included previous chemotherapy with oxaliplatin, capecitabine, or 5-FU, previous radiation to the pelvis, previous surgery for anal cancer excluding previous biopsy, known history of allergic hypersensitivity to platinum-containing compounds, peripheral neuropathy of Grade $\geq$2 according to Common Toxicity Criteria for Adverse Events version 3.0, uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, inability to take oral medication, pregnant women, HIV-positive patients, and a history of a previous malignancy (excluding nonmelanomatous skin neoplasms) during the past 5 years. Because of the known interaction of capecitabine and coumadin, patients taking coumadin were ineligible. Patients were asked to discontinue coumadin and use enoxaparin or equivalent if agreeable. Patients must have discontinued coumadin for 7 days before initiating therapy.

Procedures

Patients initially were given capecitabine (Xeloda; 825 mg/m^2 orally twice per day, Monday through Friday [M-F]), and weekly oxaliplatin (Eloxatin; 50 mg/m^2, intravenously) concurrent with radiation therapy (group 1). Chemotherapy was initially provided, M-F, for weeks 1 through 6. After the first 11 patients, the study was subsequently amended to omit chemotherapy during the third and sixth weeks of treatment (group 2; Table 1).

Treatment-related toxicities of interest included: any event resulting in Grade $\geq$3 gastrointestinal symptoms, the development of Grade 4 radiation-induced dermatitis, any event resulting in Grade $\geq$3 hematologic toxicity or nonhematologic toxicity (excluding Grade 3 radiation dermatitis), and toxicities resulting in treatment delay of chemotherapy or radiation therapy for $>$7 days. The specific management of treatment-related toxicities was previously determined.

A multidisciplinary team (medical oncologist, surgeon, and radiation oncologist) was involved in all aspects of the patient's treatment. Patients were required to have weekly physician visits including laboratory tests during the course of radiation therapy with the medical oncologist and radiation oncologist. Patients were evaluated for toxicity and failure-free survival after every 10 patients, beginning the process 3 months after the 10th patient was enrolled and provided treatment. Clinical complete response (CR) was determined by the multidisciplinary team, inclusive of laboratory tests, physical exam, repeat diagnostic imaging, and proctosigmoidoscopy at 8 to 10 weeks. Proctosigmoidoscopy was repeated at 12 to 14 weeks if there was clinical evidence of incomplete clinical response of the primary tumor. Repeat diagnostic imaging at 12 to 14 weeks was completed if there was evidence of residual tumor or lymphadenopathy on the first post-treatment imaging study. Confirmatory diagnostic imaging of CR was not required at 4 weeks. Clinical examination to evaluate for tumor recurrence was performed every 12 weeks for a maximum of 2 years. If a patient had discontinued in the study with no documented disease progression and no subsequent anticancer treatment, he/she was followed every 6 months with diagnostic imaging until disease progression or for a maximum of 2 years. Local residual disease or progression of the original primary tumor without evidence of distant disease was referred back to the surgeon for consideration of salvage abdominoperineal resection (APR).

Statistical Analysis

The primary objective was to determine time to treatment failure (TTF) and treatment-related toxicities experienced when capecitabine is used in combination with oxaliplatin and concomitant

Table 2 Characteristics of Patients

Variable	Value
Median Age (Range)	55 (39-66)
Sex	
Male	4 (20)
Female	16 (80)
ECOG	
0	14 (70)
1	6 (30)
Stage	
IIA	8 (40)
IIB	2 (10)
IIIA	6 (30)
IIIB	0
IIIC	3 (15)
T	
2	14 (70)
3	5 (25)
N	
0	8 (40)
1	9 (45)

Data are presented as n (%) except where otherwise noted.
Abbreviation: ECOG = eastern Cooperative Oncology Group.

radiotherapy. Treatment failure was defined by the development of disease persistence or progression, disease recurrence, or treatment-related mortality. Secondary objectives included the CR rate, locoregional control, colostomy-free survival (CFS), and overall survival (OS) at 2 years. We established a null hypothesis $p \leq .05$ and an alternative hypothesis $p \geq .20$, where p represents the percentage of patients with a partial or complete radiographic response to the combined treatment. The intended target accrual was 60 patients. We calculated 95% confidence intervals (CIs) around proportions using an exact binomial calculation. All analyses were done on the intention to treat population. We estimated TTF and OS using Kaplan–Meier analyses. We calculated 95% CIs around median survival outcomes using the Greenwood formula. We calculated the percentage of patients with durable responses as the number of patients with a documented radiographic response lasting past the first detection of partial or CR, relative to the total number of patients who achieved a radiographic response. Adverse events were recorded and tabulated according to type and grade. We analyzed data using GraphPad Prism for Windows, version 6.00.

Results

Between the years of 2004 and 2008, a total of 20 patients were enrolled. The median age was 55 years old. Most of our population was comprised of women and patients with node-positive disease (Table 2). Because of slow patient enrollment, the study was closed prematurely. All patients were evaluated for toxicity, but only 19 patients were considered evaluable for response. Seven of the first 11 patients (group 1) enrolled with the original chemotherapy dose developed Grade 3 gastrointestinal toxicities (12 adverse events; Table 3). No Grade 4 toxicities occurred. Consequently, the study was amended to omit chemotherapy during weeks 3 and 6. This omission of chemotherapy during radiation therapy during week 3 was on the basis of results of the phase I/II study of XELOX-XRT in adenocarcinoma of the rectum.[13] Subsequently, 9 additional patients (group 2) were enrolled after the amendment to the chemotherapy regimen, and after that, only 2 patients developed Grade 3 gastrointestinal symptoms. Ten of the initial 11 patients developed peripheral neuropathy, without occurrence of Grade 3 events. After the protocol amendment with modification of the dose of oxaliplatin, only 1 patient of 9 presented with peripheral neuropathy (Table 3).

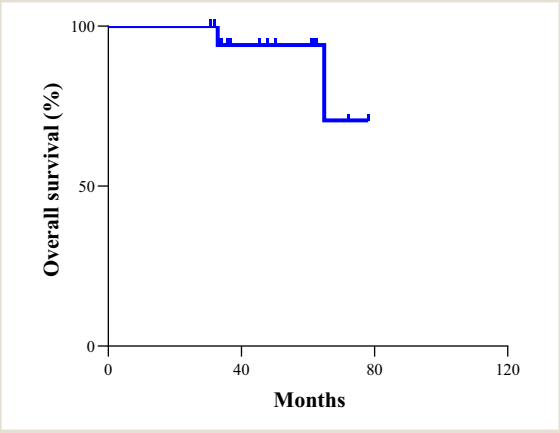
The median radiation therapy dose was 55 Gy (range, 45-59.2 Gy). All patients except 1 received a dose of at least 54 Gy. Radiation was given using 3-D conformal radiation therapy (3DCRT) in 12 patients, and intensity modulated radiation therapy (IMRT) in 8 patients. The 3DCRT technique consisted of anterior and posterior fields to the pelvis with 30.6 Gy, followed by 3 fields (posterior and laterals) with a cumulative dose of 45 Gy, followed by a boost to the grossly involved areas, with a cumulative dose of either 55 (n = 4) or 59 (n = 7) Gy, in 30 to 32 fractions. The final boost was not given in 1 patient. In 2 patients, supplemental electron fields were administered to involved inguinal regions. The IMRT technique consisted of simultaneous integrated boost, with a dose of 54 to 54.9 Gy to the primary and 45 Gy to the elective nodal region in 27 to 30 fractions (n = 7), or 59.2 Gy to the primary and 50 Gy to the elective nodal region in 32 fractions (n = 1).

Table 3 Treatment-Related Toxicities

	Any Grade		Grade 3	
Adverse Event	Group 1, n (%)	Group 2, n (%)	Group 1, n (%)	Group 2, n (%)
Dehydration	1 (8)	0 (0)	1 (11)	0 (0)
Diarrhea	5 (42)	1 (11)	5 (56)	1 (11)
Fatigue	1 (8)	0 (0)	1 (11)	0 (0)
Hemoglobin	1 (8)	0 (0)	1 (11)	0 (0)
Nausea	0 (0)	1 (11)	0 (0)	1 (11)
Pain (Abdomen NOS)	1 (8)	0 (0)	1 (11)	0 (0)
Pain (NOS)	2 (17)	0 (0)	2 (22)	0 (0)
Pain (Perineum)	1 (8)	0 (0)	1 (11)	0 (0)
Sensory Neuropathy	10 (91)	1 (11)	0 (0)	0 (0)

Abbreviation: NOS = not otherwise specified.

Figure 1 Overall Survival



After a median follow-up of 47.6 months, the median survival of our population has not been reached (Figure 1). The 3-year TTF, the primary end point, was 90.0%. There was no significant difference between group 1 and 2 (90.9% vs. 88.8%; hazard ratio [HR], 1.02; 95% CI, 0.07-13.46; $P = .984$; Figure 2). The clinical CR rate of the primary tumor at 12 to 14 weeks was 100% in group 1 and 100% in group 2, respectively (Table 4). The 3-year CFS was 90.0%, with no significant difference between groups (100% vs. 77.7%; HR, 0.10; 95% CI, 0.006-1.64; $P = .107$). One patient in group 1 developed distant disease to the liver 10 months after the completion of chemoradiation therapy. Re-evaluation of the original baseline CT scan of the abdomen/pelvis revealed nonspecific findings in the liver, which were underappreciated, suggesting early evidence of metastatic disease. Another patient developed a second microscopic primary SCCA of the anal canal (<1 mm focus) 3.6 years after completing initial therapy. The patient was re-treated with chemoradiation therapy and remained

Figure 2 Time to Treatment Failure

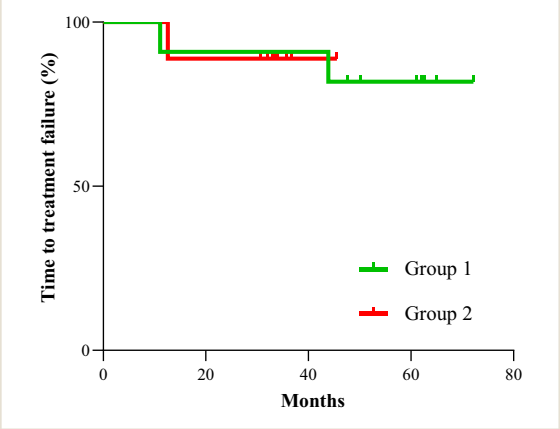


Table 4 Efficacy Analysis

Clinical Response	n
Complete Response	19 (100%)
Partial Response	0
Stable Disease	0
Progressive Disease	0
Recurrence	3
Salvage Treatment	3
Palliative Systemic Therapy	1

disease-free for 22 months but then underwent an APR 3 months after reirradiation because of persistence of recurrent invasive squamous cell carcinoma. One additional patient with poorly differentiated histology developed biopsy proven locally recurrent disease at the primary site at 11.7 months, and underwent APR. To date, both of these patients remain disease-free after salvage APR.

Discussion

As the incidence of SCCA continues to rise,[5,6] new treatment options should be pursued. Our analysis showed that XELOX-XRT is a promising regimen with significant efficacy. The treatment of locally advanced SCCA has remained largely unchanged for 3 decades, with 5-FU and MMC and concurrent radiation therapy remaining the standard of care.[2-4,7] The combination cisplatin and 5-FU with radiation has also been proven successful in treatment of this disease. However, it is essential to propose alternatives to these regimens because of their well known toxicities. Likewise, these studies were largely done in the era during which immunosuppressed patients were not eligible for enrollment.

The novelty of our regimen shows the clinical benefits of oxaliplatin as a radiation sensitizer, which might be advantageous in an immunosuppressed patient or a patient at risk for worsening renal insufficiency. Furthermore, this regimen provides an oral chemotherapy option with capecitabine, which is efficacious with added patient convenience. Moreover, likely because a low cumulative dose of oxaliplatin (300 mg/m^2 initially, then modified to 200 mg/m^2), we observed a reduced degree of peripheral neuropathy than those usually found in the management of colorectal cancer.[14,15] The increased toxicity observed with the XELOX regimen in our study in the initial phase has been previously described in clinical trials that evaluated oxaliplatin used in combination with radiation therapy in rectal cancer patients on a weekly basis,[9,11,12,16,17] mainly diarrhea. The latter noted in the first cohort of patients showed the limitations and toxicity of performing weekly oxaliplatin treatment in these patients. However, after the amendment because of toxicity, our results indicated XELOX to be a favorable regimen with tolerable toxicities as noted in cohort 2. On the basis of these data, if weekly oxaliplatin treatment is used with concurrent radiation therapy, careful attention should be provided to the proposed interval between weekly doses because toxicity might escalate.

The efficacy and safety of capecitabine have been compared with 5-FU in the management of localized anal cancer in previous studies. The oral fluoropyrimidine with MMC concurrent with radiotherapy has been associated with higher rates of dermatological toxicity,[18,19] but with lower rates of hematological toxicity and

stomatitis.[19,20] Those studies have not shown a difference in efficacy between capecitabine and 5-FU treatment.[18-20]

It is well known that SCCA responds extremely well to chemoradiotherapy. Nevertheless, it is worth pointing out the high rate of efficacy observed in our study. We performed response evaluation 12 to 14 weeks after the completion of combined modality therapy. Current evidence suggests that more conclusive response evaluation should be performed at 26 weeks.[21] At 12 to 14 week and at 26 weeks, we observed 100% rate of CR. In larger randomized clinical trials, objective response rates between 85% and 92% were reported.[2,21,22] In similar phase II trials objective response rates in the range of 65% to 96% have been reported.[23-31] The efficacy observed in our study might be overestimated because of the small sample size. However, the reported TTF (3-year 90%) is greater than those described in the largest studies,[2,21,22] as well as CFS (3-year 90%).[2-4,22] Because of the demonstrated equivalent efficacy between cisplatin and oxaliplatin in gastrointestinal malignancies[32-35] and on the basis of the striking efficacy revealed in our study, it is reasonable to propose that the XELOX regimen should be explored in larger trials as an alternative regimen in the combined treatment of SCCA.

Historically, because of the rarity of the disease, developing clinical trials in localized SCCA has been a challenge. Furthermore, previous trials excluded HIV-positive patients. Unfortunately, one of the largest limitations of our study was the premature closure resulting in a small sample size as well as the exclusion of HIV-positive patients. Recently increased recognition regarding the increasing annual incidence of anal cancer has resulted in the development of novel trials in locally advanced and metastatic disease.

Conclusion

To date, our study is the first prospective study to show the feasibility of oxaliplatin-based treatment in locally advanced anal cancer. Larger randomized clinical trials have established 5-FU with MMC as the treatment of choice with concurrent radiation therapy in early stage disease or 5-FU with cisplatin as the primary alternative.[2-4] The XELOX regimen might be considered as a promising alternative regimen. The findings of our XELOX-XRT study support the pursuit of this chemotherapy regimen as well as investigative pursuits other than 5-FU with MMC for the treatment of locally advanced SCCA.

Clinical Practice Points

- Standard of care for locally advanced SCCA involves the use of infusional 5-FU combined with MMC or cisplatin concurrent to radiation therapy, which is an inconvenient regimen, and potentially associated with chemotherapy-related myelotoxicity or nephrotoxicity, respectively.
- Herein we presented a single-arm, phase II trial, with treatment-naive locally advanced SCCA patients, to evaluate the feasibility of a more convenient regimen, XELOX-XRT.
- Complete response and 3-year time to treatment failure rates were 100% and 89.5%, respectively, in the 20 patients enrolled. Grade 3 toxicity rate was 63% in the first patients, but it decreased to 22% after adjustments in the treatment schedule.
- The XELOX-XRT regimen should be explored in larger trials as an alternative regimen for the treatment of locally advanced SCCA.

Disclosure

The study was designed by the investigators. The sponsor for this protocol was Sanofi-Aventis, which did not have a role in writing the article. The corresponding author had full access to all of the data and the final responsibility for the decision to submit for publication. The authors have stated that they have no conflicts of interest.

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