Comparison of intravenous 5-Fluorouracil with Oral Capecitabine in the Treatment of Anal Squamous Cell Carcinoma Using Modern Radiation Techniques

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ABSTRACT **Background:** Anal squamous cell carcinoma (ASqCC) is a rare malignancy, traditionally treated with combined chemoradiation, with a continuous infusion of 5-fluorouracil (5-FU) and mitomycin C (MMC). Replacing intravenous (IV) 5-FU with oral capecitabine (oral fluoropyrimidine) has been reported as a non-inferior treatment option. However, these data are scarce, with variable results.

Objectives: To examine the outcome of patients with ASqCC treated with either IV 5-FU or capecitabine concomitantly with radiation therapy. To compare treatment side effects, local recurrence, and general outcome.

Methods: We reviewed charts of patients who were diagnosed with stage I–III ASqCC. All participating patients received chemoradiation at the Assuta Medical Center between 2011 and 2019.

Results: In this study, 43 patients with ASqCC were eligible; 14 received 5-FU and 29 were treated with capecitabine. Basic characteristics were similar between the two groups, with longer follow-up for the 5-FU group. Six months following treatment, 100% (13/13 with adequate follow-up) of the 5-FU group had complete clinical response, compared to 84% in the capecitabine group (21/24), $P = 0.143$. The local recurrence incidence was higher in the 5-FU group at 23% (7, 10, 26 months following therapy, and none in the capecitabine group ($P = 0.088$). Although local and hematological toxicities were similar between groups, one patient receiving capecitabine died during chemoradiotherapy.

Conclusions: Oral capecitabine demonstrated non-inferior disease control in ASqCC treated with chemoradiotherapy. We recommend oral capecitabine over continuous IV 5-FU in locally and locally advanced ASqCC. Close monitoring of side effects is required to reduce major toxicity.

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KEY WORDS: 5-fluorouracil (5-FU), anal squamous cell carcinoma (ASqCC), chemoradiation, capecitabine, dihydropyrimidine dehydrogenase (DPD)

Anal squamous cell carcinoma (ASqCC) is a relatively rare malignancy with a reported rate of 1.9 cases per 100,000 according to the U.S. Surveillance, Epidemiology, and End Results (SEER) cancer registry, 2013–2017. The incidence of anal cancer has increased in the past few years in both sexes, regardless of human immunodeficiency virus (HIV) status, with most ASqCC tumors diagnosed in the localized or locally advanced stage [1]. Caucasian women are at greater risk compared to the general population [2]. Current research results have found ASqCC to be associated with human papillomavirus (HPV) infection [3], other HPV and HIV related malignancies [4] and lifetime multiple sex partners [5]

In just four decades, treatment has evolved from abdominoperineal resection (APR) with lymph node dissection to radiotherapy alone [6], to concomitant chemoradiotherapy with the aim of maintaining or increasing response rates while preserving function of the anal sphincter. The common treatment today in ASqCC is chemoradiotherapy, first suggested by Nigro and colleagues [7,8]. Those authors reported several series of patients with locally advanced ASqCC treated with concomitant radiotherapy and a continuous intravenous (IV) infusion of 5-fluorouracil (5-FU, 1000 mg/m²) in days 1–4 and 29–33 of radiation therapy, in addition to mitomycin C (MMC) on day 1 (IV bolus, 10–15 mg/m²). In later years, second dose was added on day 29). The initial study planned neo-adjuvant chemoradiation followed by surgical resection. There was a high rate of pathological complete response and no local recurrences. It was, therefore, suggested to intensify the radiotherapy and avoid mutilative surgery. Since then, large-scale clinical trials have established the superiority of chemoradiotherapy compared to radiation therapy alone, thus avoiding surgery in a majority of patients [9,10]. Further studies have compared MMC and cisplatin. The daily radiation dose in all studies was 1.8–2 Gy/fx, for a total dose of 50–54 Gy [11].

Capecitabine (Xeloda, Roche, Switzerland) is an oral prodrug fluoropyrimidine, and therefore does not require either central catheter insertion or in-patient hospital care. In addition,

capecitabine during all radiation therapy days increases the area under the curve, tumor exposure to fluorouracil and serves as radiation sensitizer [12,13].

Several retrospective and phase II trials in the past 10 years reported no significant differences in overall survival and locoregional failure between capecitabine and 5-FU in ASqCC and found similar toxicity levels or some minor advantages to capecitabine over 5-FU [12,14-16]. Even so, due to the rarity of the disease, only one randomized controlled trial comparing IV 5-FU and capecitabine in ASqCC has been performed [17] showing equal outcomes between the two groups. A meta-analysis published in 2016 by Souza et al. [18], which included six studies and a total of 218 patients with a median follow-up of 21.5 months, found capecitabine to be an acceptable alternative to 5-FU.

The protocol at our institution was IV 5-FU as continuous infusion, 1000 mg/m²/96 hours, with either a portable central catheter or hospitalization using a peripheral IV line, in addition to IV bolus MMC 10-15 mg/m². Since 2014, patients have received oral capecitabine (and MMC) with radiation therapy. All patients underwent a 3D computed tomography (CT) simulation and irradiated using modern radiation therapy techniques (IMRT) or volumetric modulated arc therapy (VMAT). In this article, we reported our data on these two groups of consecutive patients with ASqCC treated with curative intent with either IV 5-FU or oral capecitabine, comparing toxicity and long-term outcomes.

PATIENTS AND METHODS

PATIENT POPULATION AND DATA EXTRACTION

Following institutional review board approval, the prospectively updated database of the radiation unit at the Assuta Oncology Institute was queried for patients who were diagnosed with ASqCC and treated with chemoradiotherapy with capecitabine or 5-FU between 2011–2019. Clinically relevant data were collected from medical and radiation records. Inclusion criteria were biopsy-proven ASqCC treated with radiation therapy and concomitant chemotherapy. Clinical stage was evaluated by manual digital rectal examination, and 95% of the patients underwent ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (^{18}F-FDG PET/CT) or a chest-abdomen-pelvis CT-scan with IV contrast at baseline for staging.

TREATMENT DETAILS AND OUTCOME EVALUATION

We extracted data on the chemotherapy and radiotherapy planned doses and compared them to the recorded received treatment, as documented in the physician and nurse notes. Treatment breaks, acute toxicities, and no-shows were also obtained. Acute toxicities were scored according to the CTCAE V. 4.0 guidelines [19].

Locoregional recurrence (LRR) was defined as recurrent or persistent disease within the anal canal, inguinal, or pelvic nodes. Distant metastatic disease was defined as disease outside the pelvic.

STATISTICAL ANALYSIS

Patient characteristics, treatment details, and toxicities were summarized for each group using descriptive statistics. Pearson chi square (Fisher's exact) was used to compare nominal variables across the two groups and Mann-Whitney U test was used for continuous variables. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

Forty-three patients with localized ASqCC were included in this report. Patient characteristics were similar between the two groups, excluding follow-up time, which was longer in the 5-FU group (mean 28 months vs. 58 months, $P = 0.008$). In both groups, most patients were female and diagnosed at stage II–III. Patient, tumor, and treatment details are presented in Table 1.

The capecitabine group included 29 patients, with median age of 57 years at diagnosis (mean age 58 years, range 38–74). Median total capecitabine dose was 800 mg/m2 (range 555–825) twice a day during radiation therapy days. Side effects are summarized in Table 2. Six patients (20%) had dose reduction, and two had one-day treatment break. One patient died during radiation therapy.

The 5-FU group included 14 patients, with median age at diagnosis of 60 years (mean age 56 years, range 31–80). Patients in this group were treated with standard 96-hour continuous IV infusion of 5-FU on days 1–4 and 29–32 of the radiation therapy treatment, with 1000 mg/m2/day, no dose reduction documented. One patient received 500 mg/m2/day due to her old age (80 years) and associated co-morbidity, and one received 700 mg/m²/day.

All patients underwent CT simulation in the supine position and were treated with IMRT/VMAT plans. The prescribed dose of 45–46 Gy to the pelvis was delivered in daily doses of 1.8–2 Gy/fx. An anal boost to a mean dose of 9 Gy (4–14.4 Gy) was given to 98% of the patients and when inguinal nodes were ^{18}F-FDG avid on ^{18}F-FDG PET/CT or enlarged on CT scan (65% of the patients, 58% in the capecitabine group and 78% in the 5-FU group) the prescribed dose was 54 Gy. There was no difference between the groups for these characteristics.

TOXICITY

Perineal and perianal radiation dermatitis associated with pain during defecation and mucoid discharge was reported by 100% of the patients in the 5-FU group, and by 93% of the capecitabine group (P = NS). Patients were advised to take analgesics,

Table 1. Patient, tumor, and treatment details

Characteristic	Capecitabine	5-fluorouracil	All	*P*-value
Number	29	14	44	
Median age at diagnosis, years (range)	57 (38–74)	60 (31–80)	58 (31–80)	NS
Female	29 (97%)	11 (79%)	40 (91%)	0.088
Ever smoker	10 (33%)	4 (29%)	14 (32%)	0.884
Stage	0.151			
Stage I	4 (13.3)	1 (7.1)	5 (11%)	NS
Stage II	11 (36.7)	5 (36)	16 (36%)	NS
Stage III	15 (46)	8 (57)	23(52%)	NS
ECOG				
0	97%	93%	95%	NS
1	3%	7%	5%	NS
Known human immunodeficiency virus status	1 (3%)	1 (7%)	2 (4%)	
Dose (median)	800 mg/m^2 twice daily	1000 mg/m^2		
Chemotherapy treatment break (events)	7 (24%)	NA		0.04
Received/planned mitomycin C				
#1	29/29 (100%)	13/13 (100%)		NS
#2	11/15 (73%)	13/13 (100%)		NS

Table 2. Toxicity

	Capecitabine, n=29	5-fluorouracil, n=14	*P*-value
Radiation dermatitis			
Grade II–III	93%	100%	1.000
Unknown grade	7%		
Hematologic toxicities			
*Thrombocytopenia	7/29 (24%)	0/29	0.078
*Leukopenia	6/29 (20%)	2/29 (7%)	0.647
Neutropenia grade IV	1/29 (3%)	0/29	1.00
Diarrhea	11/29, 38%	1/14, 7%	0.044
Grade I	4/29, 14%	0	
Grade II	5/29, 17%	1/14, 7%	
Grade III	2/29, 7%	0	

*Grade I–V

use topical steroid creams, and soak in lukewarm baths. Toxicity data (gastrointestinal, hematological) are presented in Table 2. There were no reports of plantar planner erythema, oral mucositis, or urinary symptoms.

One patient in the capecitabine group died during treatment. Following 8 days of capecitabine and radiation, she presented with grade IV diarrhea, grade IV thrombocytopenia, and grade IV neutropenia. During hospitalization, she developed sepsis and multi-organ failure and died. Dihydropyrimidine dehydrogenase (DPD) was unknown.

OUTCOME

Following treatment, patients were seen for a first month follow-up and every three months thereafter. Five patients were not available for evaluation of disease control and one patient died during treatment. The outcome data includes patients with a minimum of 3 months follow-up. We evaluated complete clinical response 6 months following the end of chemoradiotherapy.

Six months following treatment, 100% (13/13 with adequate follow-up time) of the 5-FU group had complete clinical response, compared to 84% in the capecitabine group (21/24), $P = 0.143$. All three patients who did not achieve complete clinical response were diagnosed at stage 3C disease, with pelvic involved lymph nodes at diagnosis. However, the local recurrence (after chemoradiotherapy) incidence was 21% (three patients) in the 5-FU group (7, 10, 26 months following radiation therapy), and 0% in the capecitabine group ($P = 0.088$). Two of the patients with local recurrence after clinical complete response were diagnosed at stage 3C, and one of them developed metastatic disease. Another patient with N0 at presentation had local recurrence following chemoradiation.

During the follow-up period, one patient from the capecitabine group, diagnosed and treated for breast cancer prior to the

Table 3. Outcomes*

	Capecitabine, n=24	5-fluorouracil, n=13	*P*-value
Follow-up time (months)	28	58	0.008
Complete clinical response in 6 months	21/24 (84%)	13 (100%)	0.143
Local recurrence (after clinical complete response)	0	3/13 (23%)	0.088
Distant recurrence	2/24 (8%)	0	

*5 patients from the capecitabine group and one from the 5- fluorouracil group were censored due to insufficient follow-up time, including one from the capecitabine group who died during treatment

diagnosis of anal carcinoma, died of metastatic breast cancer 3 years after radiation therapy.

The 2-year ASqCC survival was 96% and 100% in the capecitabine and 5-FU group, respectively.

DISCUSSION

We found equal disease outcome of patients treated for ASqCC with radiation therapy, MMC, and either capecitabine or IV 5-FU. When analyzing the toxicity, the capecitabine group had more treatment breaks and reported higher incidence of diarrhea. In terms of convenience, patients treated with 5-FU required either 4 or 5 days of hospitalization or central line and home infuser device, with possible IV-catheter site infection, impairment in their daily activities, and reduced quality of life. Capecitabine is an oral, easy to swallow tablet, with continuous tumor drug exposure through the whole radiation process.

Compared to published literature [16,18] all patients in this series were treated with modern IMRT known to reduce side effects compared to 3D and 2D treatment planning [20,21]. Furthermore, all patients in our study were treated according to standard 96-hour infusion of 5-FU on days 1–4 and 29–32, compared to low-dose continuous 5-FU for 31 days. Some patients were treated in previous studies.

Regarding clinical outcome, Pumpalova and associates [16] reported a similar trend regarding recurrences in patients from the 5-FU group who were more likely to present with early local recurrence while patients in the capecitabine group were more likely to have late, distant recurrence. Due to differences in follow-up time between our groups, further local recurrences may be seen in the capecitabin group in the future. Furthermore, in our series, more patients with stage 3 at diagnosis were included in the 5-FU group, naturally at higher risk for locoregional recurrence. In a grouped metanalysis by Souza et al. [18] of anal cancer treated with capecitabin and radiation therapy, the pooled analysis reported a complete response rate at 6 months of 88% in all clinical stages. This finding is in concordance to our results with 84% of chemoradiotherapy in the capecitabin arm. Their pooled analysis of overall complete response (218 patients), evaluated at different intervals, was 91% and rates of locoregional relapse varied from 3.2% to 21%. In our study, we did not see any locoregional recurrence in the capecitabin group; however, we did note 23% of locoregional in the 5-FU arm, with longer follow-up of 58 months. Most patients completed the planned radiotherapy dose and only 20% had changes in their capecitabin dose. Souze et al. [18] reported up to 55.8% of any chemotherapy interruption. As radiation technique varies between studies, as well as chemotherapy initial doses, it is not possible to compare these outcomes between studies.

One patient died during treatment with grade IV neutropenia, thrombocytopenia, and severe diarrhea, occurring 8 days after the beginning of chemoradiotherapy in the capecitabine group. The explanation for her acute toxicity reaction was most probably dihydropyrimidine dehydrogenase (DPD) deficiency. This enzyme is initiated and rate-limited in the catabolism of 5-fluorouracil. A partial or complete deficiency in DPD is associated with early and severe toxicity manifestation during 5-FU treatment, such as diarrhea, neutropenia, thrombocytopenia, and mucositis. The incidence of DPD deficiency in the general population is 3–5% for partial deficiency and 0.2–0.3% for complete deficiency [22]. Currently, the latest NCCN guidelines do not comment on routine DPD deficiency testing prior to fluoropyridine therapy [23]. To note, Boisdron-Celle et al. [24] demonstrated a statistically significant reduction in early and severe toxicity and related death prevention for patients tested for DPD deficiency prior to 5-FU treatment. Their patients had close blood pharmacokinetics monitored 5-FU. According to current EMA guidelines, patients should be tested for DPD deficiency either by measuring levels of uracil in the blood or by checking for the presence of mutation. Patients with known partial DPD deficiency should start with low doses of fluoropyrimidines (5-FU, capecitabine, tegafur) and be monitored for uracil blood levels during treatment [25]. However, timing and accessibility may be a major obstacle, delaying the start of curative chemotherapy treatment.

Capecitabine is an oral treatment; therefore, no hospital admission or central line IV catheter for continuous infusion is necessary. In the current study, diarrhea was more common in the capecitabine group, 38% vs. 7%, $P = 0.044$, but no hospitalization was needed for that reason. Since patients come daily for radiation therapy, close monitoring can be accomplished, and dose reduction/adjustment can be easily recommended when side effects appear. In our department, patients undergo weekly blood count and physician appointments, with special attention to relative leucopenia, early oral mucositis, and any signs of abdominal discomfort that might preface diarrhea. Patients are encouraged to contact the medical staff for any questions regarding treatment during the chemoradiotherapy period.

We acknowledge the limitation of this series, as it is a small, retrospective, single institution study. Long-term follow-up for the capecitabine group is warranted. However, anal cancer is a

rare disease, and there are currently no published randomized phase III studies comparing the two chemotherapy treatment options with modern radiation technique.

As many oncology-related therapies, including biological treatments (subcutaneous trastuzumab, oral CDK inhibitors) and oral chemotherapy agents (vinorelbine, capecitabine) are self-administered, hospitalization is rarely mandatory. Daycare units can provide appropriate treatment monitoring either by personal meetings or by telemedicine. Considering health economics and the high pricing of hospitalization with associated complications, ambulatory treatment is both medically effective and cost effective.

CONCLUSIONS

Oral capecitabine demonstrated non-inferior disease control; therefore, physicians should consider oral capecitabine over continuous infusion of 5-fluorouracil in locally and locally advanced anal squamous cell carcinoma. Close monitoring of side effects is required to reduce major toxicity.

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Everybody knows if you are too careful you are so occupied in being careful that you are sure to stumble over something.
Gertrude Stein (1874–1946), American novelist, poet, and playwright