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Research Article

Feasibility and Safety of 3-Weekly Carboplatin/Paclitaxel Regimen in Advanced Squamous cell Carcinoma of the Anal Canal

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ABSTRACT

Introduction: Anal cancer is a rare disease, and there is a lack of phase 3 studies in the advanced setting. Currently, the standard treatment is based on interAACT phase 2 study using Carboplatin (C) (AUC 5, D1q28) plus Paclitaxel (P) (80 mg/m2, D1,8,15q28). This study demonstrated a median OS of 20m, a response rate of 59% and serious adverse events in 36% of patients (pts). However, this regimen requires more infusions and hospital visits than a 3-weekly CP regimen, resulting in high social and financial cost.

Objective: To retrospectively access safety and efficacy of treatment with 3-weekly CP in advanced SCCA.

Methods: We performed a single-center retrospective analysis of patients (pts) who received first-line treatment with 3-weekly CP for inoperable locally recurrent or metastatic SCCA between Jun/2011 and Jun/2018. Study data were collected using REDCap®. Survival analyses were estimated with the Kaplan-Meier method and compared by log-rank test. Prognostic factors were evaluated by Cox regression.

Results: 47 patients were included. Median age was 57 years, 60% (n=28) were female and 21% (n=10) HIV positive.16% (n=7) had metastatic disease at diagnosis. The majority of pts (n=42) were treated with paclitaxel (P) 175 mg/m2 plus carboplatin (C) AUC 5 every 3 weeks. The median number of cycles was 4 and dose reduction by toxicity was necessary for 30% (n=14). Grade 3/4 adverse events were neutropenia 19% (n=9), anemia 4% (n=2), fatigue 4% (n=2), neuropathy 2% (n=1). Two pts had interruption due to toxicity and no treatment-related death. 64% of patients benefited from treatment, 4% with complete response. The median overall survival (OS) was 10 months(m). In a multivariable analysis, HIV-positive (HIV+) status (HR 3.1; 95%CI 1.8-8.4; p 0.001) and ECOG 2/3 (HR 3.9; 95%CI 1.2-8.1; p 0.01) showed a negative impact on OS. Median OS was 16m for HIV- vs 4m for HIV+ group; and 20m for ECOG 0/1 vs 4m for ECOG 2/3.

Conclusion: The present study suggests that 3-weekly CP has similar outcomes to the InterAACT regimen. Nevertheless, pts who are HIV+ or have ECOG 2/3 had poor outcomes and other treatment strategies should be studied for these pts.

Introduction

Anal cancer is a rare disease, but the incidence in underdeveloped countries is increasing by 2% a year [1]. The predominant histological type is squamous cell carcinoma (SCC), and relevant risk factors related to SCC are infection with human papillomavirus (HPV) and immunosuppression [2]. Most patients have a local disease at initial diagnosis, but 10%-30% will develop recurrent disease after chemoradiotherapy.

Patients with no curative therapeutic options are treated with chemotherapy, typically containing platin. Overall survival in this setting with systemic treatment in one-year and 5-year is 60% and 32%. HIV positive patients are more likely to experience a significant complication of oncologic treatment and have less chance of response,

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which leads to a worse prognosis [3, 4]. The InterAACT phase II study enrolled 91 patients and established the standard care of treatment, carboplatin (C) q28d plus weekly paclitaxel (P) [5]. However, in daily practice, especially in underdeveloped countries, the patients have difficulties coming weekly to the hospital for oncologic treatment. In this setting, this study evaluated the safety and efficacy of 3-weekly CP in advanced anal SCC.

Methods and Materials

We performed a single-center retrospective analysis of anal SCC patients submitted to first-line chemotherapy regimen with 3-weekly carboplatin and paclitaxel. The patients were treated between June/2011 and June/2018 at Instituto do Câncer do Estado de São Paulo (ICESP), Brazil. Eligible patients have metastatic disease or inoperable local recurrence. We reviewed all electronic medical records, laboratory tests, and images available. The study data was collected using RedCap®.

The data were summarized with descriptive statistics. Overall survival (OS) was the primary endpoint, defined from C1D1 chemotherapy until the date of death from any cause. The Kaplan-Meier method estimated survival functions, and the log-rank test compared survival curves. Factors associated with OS were evaluated with univariable and multivariable Cox regression. Objective response rate (ORR) and toxicity were secondary endpoints. The laboratory results were classified by Common Terminology Criteria for Adverse Events (CTCAE) v.4.03. A radiologist specialist in gastrointestinal tumors reviewed all images and performed RECIST v1.1.

Results

We included 47 patients, the median age was 57 years; 60% (n=28) were female, and 21% (n=10) HIV positive. At initial diagnosis, 62% (n=28) were IIIB, and 16% (n=7) already had distant metastatic disease. The characteristics of the patients are presented in (Table 1). The majority of patients (n=42) were treated with paclitaxel (P) 175 mg/m2 plus carboplatin (C) AUC 5 every three weeks. In the C1D1 timepoint, 62% had distant metastasis. The median number of cycles was 4. The median overall survival of the entire cohort (OS) was ten months (m). Among HIV positive group (n=10), seven patients had progression, two stable diseases, and one was non-evaluable. Considering the ECOG 2/3 group (n=15), two had a partial response, ten disease progression, one stable disease, and two were non-evaluable.

Table 1: Patients Characteristics.

Median age	57 years	
	n	%
Sex		
Female	28	60
Male	19	40
Race		
White	35	74
Black	4	09
Other	8	17
ECOG		
0	12	26
1	19	40
2	10	21
3	6	13
HIV status		
Positive	10	21
Negative	35	75
Unknown	2	04
Clinical stage at diagnosis (AJCC VII)		
I	1	02
II	6	13
IIIA	3	07
IIIB	28	62
IV	7	16

In a multivariable analysis, HIV positive (HIV+) status (HR 3.1; 95%CI 1.8-8.4; p=0.001) and ECOG 2/3 (HR 3.9; 95%CI 1.2-8.1; p=0.018) showed a negative impact on OS (Table 4). Median OS was 16m for HIV- vs. 4m for HIV+ group; and 20m for ECOG 0/1 vs. 4m for ECOG 2/3 (Figures 1 & 2, respectively). Regarding objective response rate, one patient had a complete response, 20% (n=10) had a partial response, 30% (n=13) stable disease, 38% (n=19) disease progression, and 5 were non-evaluable (Table 3). Dose reduction by toxicity was necessary for 30% (n=14) (Table 2), among these patients n=10 was in HIV- group and 4 in HIV+ group. Grade 3/4 adverse events occurred in 14 patients, with neutropenia 19% (n=9), anemia 4% (n=2), fatigue 4% (n=2), and neuropathy 2% (n=1). Two patients had treatment interruption due to toxicity, all of them in HIV+ group. No treatment-related death occurred. Clinical benefit was reported in 64% (n=32).

Table 2: Treatment Characteristics.

	n	%
Surgical rescue		
Yes	5	11
No	42	89
Median number cycles	4	
Dose reduction by toxicity		
Yes	14	30
No	33	70
Discontinuation by toxicity		
Yes	2	04
No	45	96
Re-treatment with CP		
Yes	6	22
No	21	78
Second line		
Yes	12	26
No	35	74
Third line		
Yes	3	6
No	44	94
Toxicity G3/4		
Global	14	29
Neutropenia	9	19
Anemia	2	04
Fatigue	2	04
Neuropathy	1	02

Table 3: Response Rate by RECIST 1.1.

	n	%
Complete Response	1	02
Partial Response	10	20
Progressive disease	19	38
Stable Disease	13	30
N/A	5	10

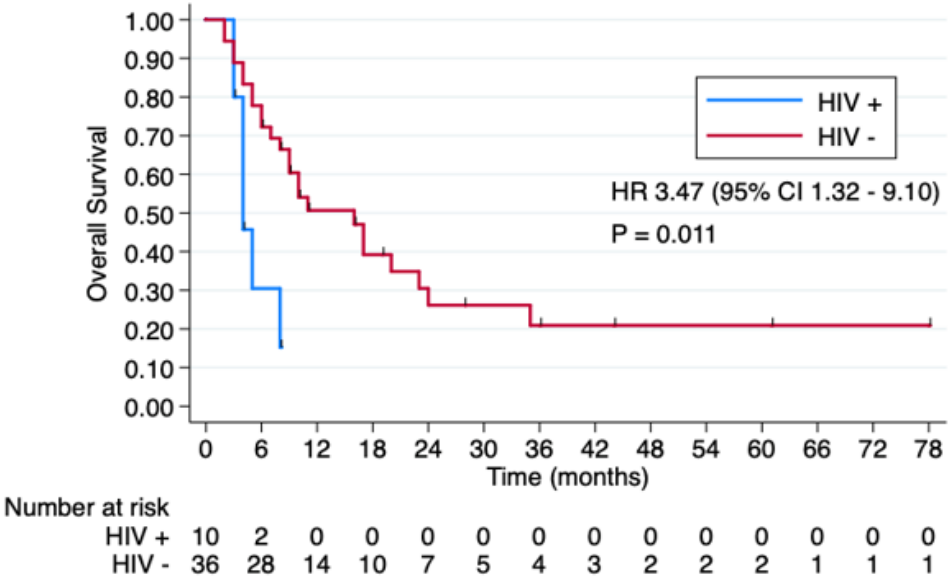

Figure 1: Overall survival curves according to HIV status.

Table 4: Factors associated with overall survival.

	Univariable analysis		Multivariable analysis	
	HR (95% CI) [1]	**P value**[1]	**HR (95% CI)** [1]	**P value**[1]
Age (> 60 vs < 60 years)	0.66 (0.32-1.35)	0.264	-	-
HIV (positive vs negative)	3.47 (1.32-9.10)	0.011	3.92 (1.81-8.49)	0.001
ECOG (2-3 vs 0-1)	4.07 (1.88-8.81)	<0.001	3.15 (1.22-8.14)	0.018
Dose reduction (yes vs no)	1.01 (0.47-2.15)	0.976	-	-

HR: Hazard Ratio; CI: Confidence Interval; HIV: Human Immunodeficiency Virus; ECOG: Eastern Cooperative Oncology Group performance status.
[1]Cox regression.

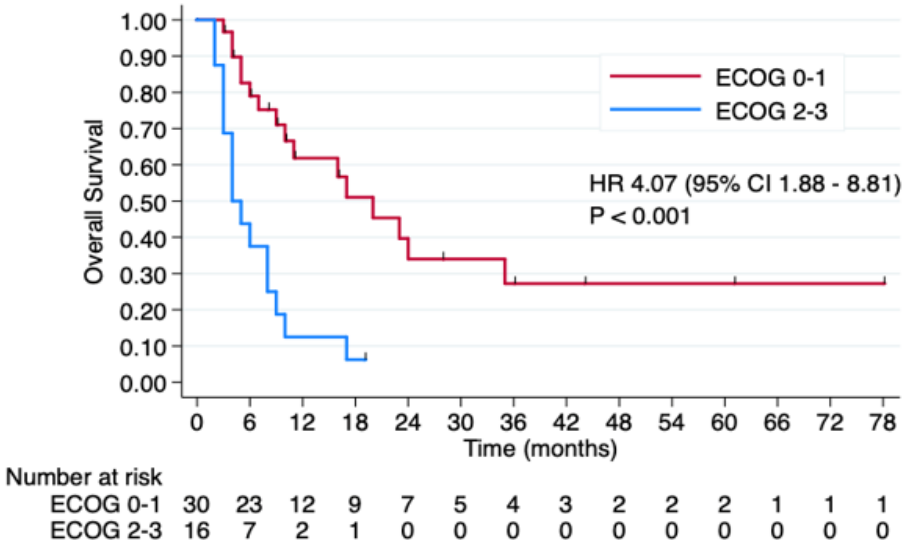

Figure 2: Overall survival curves according to ECOG performance status.

Discussion

The phase II study InterAACT showed a median 20m OS with 59% of objective response in the CP group. Considering only the ECOG 0/1 population, the same OS was achieved with the 3-weekly regimen. Our study included a real-life non-selected population with 21% of HIV positive and 34% ECOG 2/3 patients, which may explain the global shorter RR and OS. In a multivariable analysis, the population HIV positive had the worse outcome (HR 3.1; 95%CI 1.8-8.4; p=0.001). The median OS was 16m for HIV negative vs. 4m for the HIV positive group. Only one retrospective and heterogeneous study enrolled 18 patients treated with CP 3 weekly regime in advanced anal SCC at first to the fourth line, with a median OS of 12.1 months [6]. In our study, the toxicity grade ≥3 was lower than the InterAACT regimen (76% vs. 29%). The most frequent grade 3/4 adverse events were neutropenia 19% (n=9), anemia 4% (n=2), fatigue 4% (n=2), and neuropathy 2% (n=1). Considering HIV's previous known status population (n=45), 40% of the HIV+ population had dose reduction and 28,5% in HIV- group. All patients that interrupted treatment due to toxicity were HIV+.

Other studies reported the use of polychemotherapy in the first-line regimen for advanced anal cancer. Vincristine, bleomycin, and methotrexate (BOM) lead to an objective rate of 25%, with a median survival of 8 months and a high incidence of severe drug-related toxicity [7]. The combination of mitomycin, adriamycin, cisplatin (MAP), and bleomycin in 20 patients showed a response rate of 60%, with a median OS of 15 months with 50% of grade 3 or higher toxicity [8]. TIP regimen (paclitaxel, ifosfamide, and cisplatin) was used in 3 patients, showing complete response maintained for 4, 6, and 30 months [9]. In the phase 2 study, Epitopes-HPV02 docetaxel, cisplatin, and fluorouracil (DCF) were evaluated in 66 patients with 45% complete response with 70% of grade 3/4 toxicity [10]. The role of anti-EGFR antibodies in the first line of treatment of advanced anal SCC is still being studied; a small series reported three partial responses among seven patients treated with cetuximab alone or in combination with irinotecan [11]. The majority of data available did not cite the HIV status of the population included.

Checkpoint inhibitors are currently promising options, but the data available considers only refractory patients in the second-line or further. Nivolumab shows an ORR of 24% with a disease control rate of 72% and, pembrolizumab an ORR of 17%, and a disease control rate of 58% [12, 13]. The CP regime is often used and supported by international guidelines, such as The National Comprehensive Cancer Network, considering the polychemotherapy's toxicity profile and the lack of evidence of immunotherapy/anti-EGFR in the first-line setting. The weekly use of paclitaxel is more exhaustive and expensive than the 3-weekly CP regimen, and this study demonstrates a similar overall survival in ECOG 0/1 patients compared to weekly regimen available data, with manageable toxicity in HIV- population. As a retrospective analysis, our study has limitations. The data regarding low-grade toxicities could not be well represented; on the other hand, to our knowledge, this is the largest study with a 3-weekly CP regimen in a

locally advanced or metastatic setting anal SCC. Another essential point is the evaluation of the HIV+ population, frequently excluded in the randomized clinical trials.

Conclusion

3-weekly CP regimen is feasible and demonstrates a similar OS to the weekly regimen in ECOG 0/1 and HIV- patients with manageable toxicity. HIV+ and ECOG 2/3 population had poor outcomes and more related treatment toxicity.

Ethical Approval

This study was approved by the institutional review board and ethics committee.

Discloser

None.

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