Outcome of Immunotherapy in Advanced Cervical Cancer after Progression to Platinum-Based Therapy in the Real World

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Abstract

Introduction Cervical cancer remains a global health concern, particularly in low- and middle-income countries. Immunotherapy has demonstrated meaningful improvements in the overall survival (OS) of patients with recurrent, persistent, or metastatic disease that progressed to platinum-containing chemotherapy. The present study aimed to evaluate real-world outcomes with the use of immunotherapy in this setting.

Materials and Methods The current retrospective observational study included patients with recurrent, persistent, or metastatic cervical cancer who were exposed to single-agent immunotherapy at Oncoclínicas&CO private healthcare oncology network from July 2017 to January 2024. We performed descriptive statistics and estimated the time until treatment discontinuation (TTD) and OS through the Kaplan-Meier method.

Results In total, 60 patients met the inclusion criteria: 33 (55%) received cemiplimab, 26 (43.3%), pembrolizumab, and only 1 (1.7%), nivolumab. Most received immunotherapy as the second-line treatment (85%) after chemotherapy plus bevacizumab (64%). After a median follow-up of 12 months, the median TTD was of 6.3 months (95% confidence interval [95%CI]: 4.7–9.6), and the median OS was of 10.7 months (95%CI: 9.1–not reached [NR]).

Conclusion The present real-world study demonstrated comparable outcomes of single-agent immunotherapy for advanced cervical cancer with those described in pivotal clinical trials. These findings support the reproducibility and efficacy of immunotherapy, highlighting its role as a valuable treatment option in platinum-resistant cervical cancer.

Keywords
- uterine cervical neoplasms
- immunotherapy
- data collection

Introduction

Despite screening exams and the implementation of human papillomavirus (HPV) vaccination programs, cervical cancer is the fourth most common cancer in women worldwide, and its incidence is especially high in low- and middle-income countries.[1] In Brazil, according to the National Cancer Institute (Instituto Nacional de Câncer, INCA, in Portuguese), it represents the third most incident neoplasm in women (excluding non-melanoma skin cancer) and the

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first cause of gynecologic cancer, with 17,010 new cases estimated for 2024.[2]

In persistent, recurrent, or metastatic cervical cancer, the standard first-line treatment is platinum-based chemotherapy. If the tumor expression of programmed cell death-ligand 1 (PD-L1) by combined positive score (CPS) is ≥ 1, the association of chemotherapy with pembrolizumab is recommended, and, in case of no contraindication, bevacizumab can also be included in the treatment regimen.[3]

After progression to platinum-based chemotherapy, trials[4] evaluating checkpoint inhibitors with anti-programmed death-1 (anti-PD-1) and anti-cytotoxic T-lymphocyte-associated antigen 4 (anti-CTLA-4) agents have been conducted. Cemiplimab,[4] pembrolizumab,[5] and nivolumab,[6] anti-PD-1 agents, have demonstrated favorable outcomes in the scenario of platinum-resistant disease in patients who have not received anti-PD-1 therapy combined with chemotherapy in the first-line setting.[7,8]

These clinical trials were the key to advancing medical knowledge and improving the care of patients with advanced cervical cancer. However, they are characterized by methodological rigor to reduce bias, with strict inclusion and exclusion criteria that often result in the inclusion of patients that differ significantly from those seen in the clinical practice.[9] In this context, real-world studies have become increasingly important because they pragmatically cover a representative proportion of the population,[10] providing information about the effectiveness and the reproducibility of the trial results in a real-life population.[11]

The primary objective of the present study was to analyze the real-world outcomes of patients with advanced cervical cancer from a Brazilian private healthcare network treated with single-agent immunotherapy after progression to platinum-based chemotherapy.

Materials and Methods

The current was an observational, cohort study, with retrospective analysis of data available in the Oncoclínicas&CO data lake, representing 70 clinical sites located in 11 out of 27 federative units of Brazil. We combine longitudinal electronic health record (EHR) data in a cloud-based platform, which includes structured elements (patient demographics, disease stage, anticancer drug prescriptions) with elements from unstructured sources (such as physician notes) using technology-based abstraction techniques. Trained data curators qualify the data using predefined ontology and actively search for critical outcomes in the patient's disease trajectory, including treatment line and intent. External linkage to national death registries guarantees complete information of survival endpoints. Manual data cleaning was performed to ensure validity and quality.

The eligible patients were 18 years of age or older, presented recurrent, persistent, or metastatic disease not amenable to curative therapy, were exposed to immunotherapy as a single agent, and had undergone at least 3 months of follow-up between the start of immunotherapy and the last documented visit or death. The period for inclusion was between July 2017 and January 2024. Patients treated with immunotherapy combined with other systemic agents were excluded.

For the descriptive analysis, we expressed the categorical variables related to demographic and clinicopathological characteristics as absolute and relative frequencies, and values for the continuous variables, as median and range values. The time until treatment discontinuation (TTD) was calculated as the time elapsed between the date of treatment start and the date of discontinuation or death, while overall survival (OS) was estimated from the time of the first treatment day until death from any cause using the Kaplan-Meier method. Patients alive at the last available follow-up were censored. All data was processed in the R programming environment (R Foundation for Statistical Computing, Vienna, Austria), version 4.0.5.

Results

We included 60 patients with advanced cervical cancer who were treated with immunotherapy: 33 (55%) with cemiplimab, 26 (43.3%) with pembrolizumab, and only 1 (1.7%) with nivolumab.

The demographic and clinical characteristics of the patients are presented in ►**Table 1**. The median age was of 53 (range: 31–97) years. Most of the patients (73%) were concentrated in the Southeastern region of Brazil, 7% in the Southern, and 10% in the Midwestern and Northeastern regions. Most cases were metastatic de novo (60%), and 85% of the patients received immunotherapy as the second-line treatment. Concerning previous therapy for advanced disease, all patients received chemotherapy, in 23 (64%), it was combined with bevacizumab. Information about subsequent therapy was available for 19 patients (32%); all received chemotherapy, 2 of them in combination with bevacizumab and, in 1 patient, immunotherapy (pembrolizumab) was maintained in association with the chemotherapy and bevacizumab.

With a median follow-up of 12 months, the median TTD was of 6.3 months (95% confidence interval [95%CI]: 4.7–9.6) (►**Fig. 1**) and the median OS was of 10.7 months (95%CI: 9.1–not reached [NR]) (►**Fig. 2**).

Discussion

Patients with persistent, recurrent, or metastatic cervical cancer have a poor prognosis, especially in the setting of platinum resistance. In this scenario, immunotherapy has been shown to be a promising treatment, with improvements in progression-free survival (PFS) and OS.

The efficacy of pembrolizumab in patients with previously-treated cervical cancer was based on A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects with Advanced Solid Tumors (KEYNOTE-158),[5] a phase-2 basket study that included several types of solid tumors that progressed with the standard therapy. In the cervical cancer cohort, 98 patients were included, 83.7% of whom had PD-L1 positive tumors (CPS expression ≥ 1). In the PD-L1 positive population, the response rate was of

Table 1 Demographic and clinical characteristics of patients

Characteristic	Results
Patients – n (%)	60 (100)
Age (in years)	
Median (range)	53 (31–97)
< 65–n. (%)	42 (70)
Metastasis at diagnosis – n (%)	
Yes	36 (60)
No	15 (25)
Missing	9 (15)
Region of Brazil – n (%)	
Southern	4 (7)
Southeastern	44 (73)
Midewestern	6 (10)
Northeastern	6 (10)
Line of immunotherapy – n (%)	
Second line	51 (85)
Third line or more	9 (15)
Previous palliative therapy – n (%)[†]	
Anti-VEGF + chemotherapy	23 (64)
Chemotherapy	13 (36)
Subsequent therapy – no. (%)[‡]	
Anti-VEGF + chemotherapy	2 (11)
Chemotherapy	16 (84)
Immunotherapy + chemotherapy[§]	1 (5)

Abbreviation: VEGF, vascular endothelial growth factor.
Notes: [†]For those receiving palliative therapy in the metastatic setting; [‡]38% of the patients who underwent single-agent immunotherapy had no record of subsequent regimen use; [§]in association with anti-VEGF (bevacizumab).

14.6%, in addition to an estimated median PFS of 2.1 months and a median OS of 11 months.[5]

Cemiplimab, a fully-human anti-PD1 monoclonal antibody, was approved after progression to platinum-based chemotherapy according to An Open-Label, Randomized, Phase 3 Clinical Trial of REGN2810 Versus Investigator's Choice of Chemotherapy in Recurrent or Metastatic Cervical Carcinoma (EMPOWER CERVICAL-1).[4] Patients were randomized to receive cemiplimab or the investigator's choice of single-agent chemotherapy (the options included pemetrexed, topotecan, gemcitabine, irinotecan, or vinorelbine) regardless of PD-L1 status. The study met its primary endpoint, demonstrating a statistically significant improvement in OS: of 12 months with cemiplimab versus 8.5 months with chemotherapy (hazard ratio [HR]: 0.69; 95%CI: 0.56–0.84; $p < 0.001$). Despite the fact that the median PFS was similar in the two groups (2.8 months with cemiplimab and 2.9 months with chemotherapy), the HR indicated a significantly longer PFS with immunotherapy (HR: 0.75; 95%CI: 0.63–0.89; $p < 0.001$). The objective response rate (ORR) was of 16.4% with cemiplimab and of 6.3% in the control arm, and the median duration of response (DOR) was also better with the anti-PD1.[4]

Another checkpoint inhibitor evaluated as a monotherapy in this setting was nivolumab in the phase-1/2 trial Non-Comparative, Open-Label, Multiple Cohort, Phase 1/2 Study of Nivolumab Monotherapy and Nivolumab Combination Therapy in Subjects With Virus-Positive and Virus-Negative Solid Tumors (CheckMate 358), in which patients with squamous cell carcinoma of the cervix, vagina, or vulva received nivolumab 240 mg every 2 weeks. Patients with HPV-negative tumors were not included. In total, 19/24 randomized patients presented cervical neoplasms. Of these, 16 were quantified for PD-L1 expression through evaluation of tumor cells, 10 of whom presented tumors with PD-L1 expression $\geq$ 1%. In the cervical cohort, the response rate was of 26.3%, with a disease control rate of 68.4%.[6] Considering these results, the National

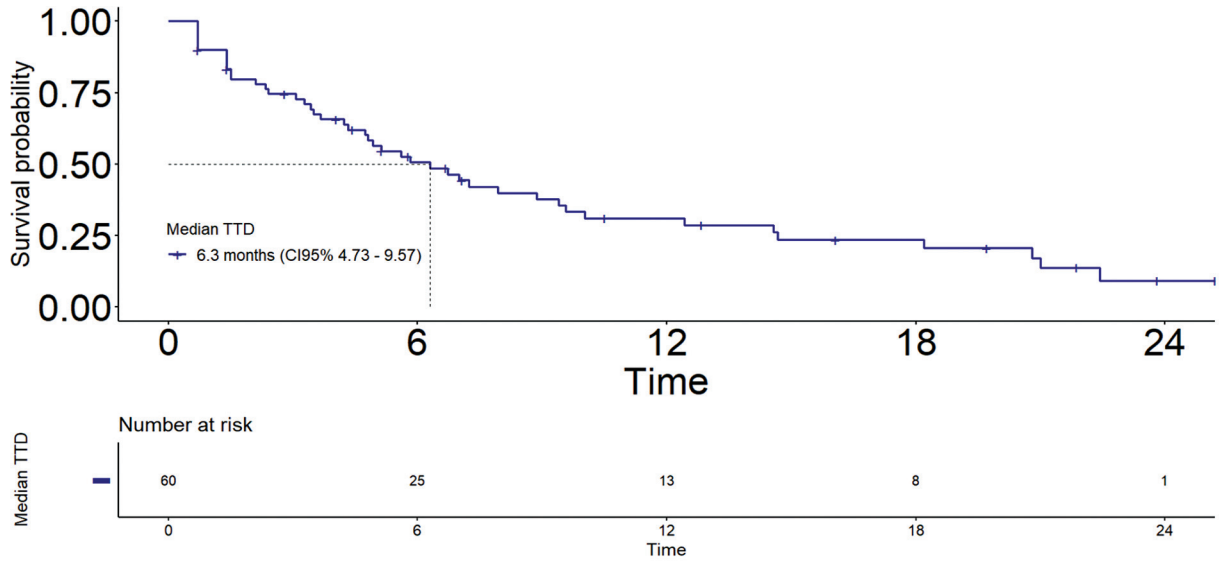

Fig. 1 Time until treatment discontinuation.

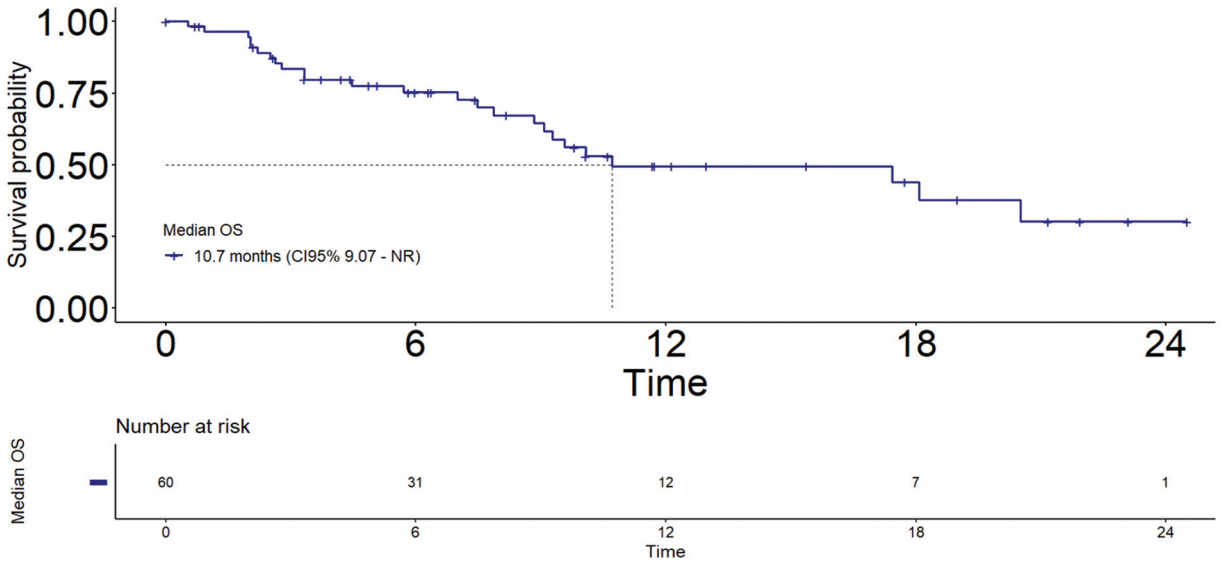

Fig. 2 Overall survival.

Comprehensive Cancer Network[12] (NCCN) also recommends nivolumab as a possible option for second-line or greater in tumors with positive expression of PD-L1.

Some of the patients included in the present real-world study would not have met the inclusion criteria of a clinical trial, such as upper age limits and other unmeasured confounders. Despite this, a comparable median OS was found when compared to the KEYNOTE-158 and EMPOWER CERVICAL-1 trials: 10.7, 11, and 12 months respectively.

The current study has some limitations, since it was based on a small sample size and retrospective analysis of EHR data, with missing information. Furthermore, it was not possible to evaluate toxicity, and TTD is not necessarily associated with disease progression, since the patient could have their treatment discontinued because of adverse events.

A strength of the present work is that, although it portrays the reality of a single private oncology center in Brazil, there are several clinics in this group distributed across the various regions and cities of Brazil country, thus reflecting a diverse population.

Conclusion

Real-world data are important because they reflect the efficacy of treatment outside of the tightly-controlled environment of randomized clinical trials, considering a more heterogeneous population. The current study demonstrated outcomes with immunotherapy for advanced cervical cancer after platinum-containing therapy that are comparable with those described in clinical trials. Despite the limitations, these results confirm the effectiveness and reproducibility of this treatment in clinical practice.

Authors' Contributions

GVG and RD: data analysis and interpretation, final approval of the manuscript, and manuscript writing; RDP and CLN: collection and assembly of data, data analysis and interpretation, and final approval of the manuscript; and ACM: conception and design, final approval of the manuscript, and manuscript writing.

Clinical Trials

None.

Ethics Committee Number

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Conflict of Interests

The authors have no conflict of interests to declare.

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