Research Article

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Carboplatin versus cisplatin: an observational study in locally advanced cervical cancer

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ABSTRACT

Background : Cisplatin-based chemoradiation is the standard treatment for locally advanced cervical cancer. However, the toxicity and prolonged infusion time associated with cisplatin urges the search for options that yield similar outcomes. Our objective is to compare the effectiveness of carboplatin versus cisplatin.

Methods : The current study is observational and retrospective, consisting of 183 patients with locally advanced cervical cancer who underwent chemoradiation treatment at the National Institute of Neoplastic Diseases, Lima, Peru, between 2014 and 2015. We analyzed their adverse events, response to therapy, disease evolution, and survival outcomes.

Results : The squamous cell carcinoma subtype represented 89.6% of the sample, and the most frequent stages were IIB (64%) and IIIC (27%). The trend for complete responses was higher for cisplatin (82%) than carboplatin (77%) but not statistically significant (p=0.3). Neutropenia, diarrhea, and vomiting were the most reported events, with the former being significantly lower in the carboplatin group (p=0.001). At a 5-year follow-up, there was a 41% reduction in the risk of progression and a 28% reduction in risk of death in favor of cisplatin treatment (PFS: HR 0.59, 95% CI 0.34-1.00, p=0.055 and OS: HR 0.72, 95% CI 0.33-1.57, p=0.4). Generally, it was observed that those who achieved a complete response had better survival (p<0.001).

Conclusions : In summary, while there are no differences in efficacy, carboplatin is slightly better tolerated. This suggests that carboplatin could be a valid alternative for patients with a more delicate clinical condition who might face challenges with cisplatin-associated toxicity.

INTRODUCTION

Cervical cancer (CC) is a persistent threat to women's health worldwide. With an incidence of 604127 new cases and around 342000 deaths in 2020, it holds as the fourth most common malignancy and the second most frequent in females (Sung et al. 2021). The higher incidence and mortality rates are found in transitioning countries (of low- and middle-income) in contrast to transitioned ones, a trend that persists even within the same nation (Sung et al. 2021; Siegel, Miller, and Jemal 2019; Payet Meza et al. 2021).

Peru is no different in this regard. In 2020, the crude incidence rate was 25.7 per 100,000 women, causing 2288 deaths, 300 more than the year before (World Health Organization 2021; Ministerio de Salud 2023). Only in Lima Metropolitan, this

cancer accounted for 9.4% of all new cases of malignancies in women and over 1300 cancer-related deaths in the 2013-2015 period, the highest incidence being in lower-income districts (Payet Meza et al. 2021). Although incidence and mortality have lowered from previous decades (Siegel, Miller, and Jemal 2019; Payet Meza et al. 2021), these numbers remain worrisome, especially since CC is considered preventable in nearly its totality (Sung et al. 2021; Ministerio de Salud 2023).

The treatment strategy is dictated by the International Federation of Gynecology and Obstetrics (FIGO) classification, which consists of surgery, radiotherapy, and/or chemotherapy, depending on the stage and functional status of the patients (Bhatla et al. 2021). In early-stage disease, the primary treatment is surgery. For patients with locally advanced cervical cancer (LACC), all international guidelines recommend concomitant platinum-based chemoradiation at the pelvis level followed by brachytherapy (BT) (Bhatla et al. 2021; Cibula et al. 2018). Platinum complexes are widely used to treat cancer (Ahmad 2017). Cisplatin is the first generation of platinum-based anticancer drugs, discovered in the late 1960s and approved by the FDA a decade later (Alderden, Hall, and Hambley 2006). It is a nonspecific therapeutic drug that enters tumor cells through diffusion and via Cu-transporting proteins, binding itself to the DNA to cause apoptosis (Alderden, Hall, and Hambley 2006; Ahmad 2017). However, cisplatin is associated with gastrointestinal problems, hearing problems, nephrotoxicity, neurotoxicity, vascular toxicity, and urinary complications, among other adverse events, with geriatric patients being more susceptible (Alderden, Hall, and Hambley 2006; Ahmad 2017; Jacobson et al. 2005; Pötter et al. 2007; Food and Drug Administration 2021). Additionally, some patients may develop resistance to cisplatin over time, while others may not complete treatment because of comorbidities, infections, or cisplatin intolerance, which in turn causes higher recurrence and worse survival outcomes (Alderden, Hall, and Hambley 2006; Food and Drug Administration 2021; Kotha et al. 2022).

In consequence, carboplatin was developed as a second-generation platinum chemotherapy. Compared to its predecessor, carboplatin shows a lower hydration rate due to bidentate cyclobutene-dicarboxylic acid ligands and has higher biosafety with significantly reduced systemic toxicity (Ahmad 2017; Alderden, Hall, and Hambley 2006). It has shown high rates of achieved complete response with a low chance of recurrence and adequate-to-comparable survival outcomes, alongside fewer and less severe toxicities (anemia, neutropenia, and nephrotoxicity) than cisplatin, allowing for better patient compliance (Katanyoo et al. 2011; Kitagawa et al. 2015; Tharavichitkul et al. 2016; S. Hu et al. 2023).

In the Peruvian context, high incidence and lack of specialized health centers make it difficult to meet the treatment demand with cisplatin as the primary treatment, given its toxicity and prolonged infusion time (Food and Drug Administration 2021). Therefore, we evaluated the equivalence in toxicity and efficacy between carboplatin and cisplatin treatment, concurrent with radiotherapy of LACC patients, to propose a safe and efficient alternative to cisplatin in our reality.

METHODS AND MATERIALS

Study design and setting

This is an observational, retrospective, and longitudinal study. It intends to describe and compare the outcomes of two platinum-based treatments for CC. The scope is the Instituto Nacional de Enfermedades Neoplásicas (INEN), Lima, Peru, a national reference center for oncology patients. We retrospectively analyzed the clinical records of 250 patients diagnosed with LACC from January 1, 2014, to December 31, 2015.

Eligibility criteria

Inclusion criteria include a certain minimum age (over 18 years) and treatment of the patients at INEN. We only included patients with a confirmed diagnosis of LACC who received treatment with chemotherapy (carboplatin or cisplatin) concurrent with radiotherapy during 2014-2015. We excluded patients who were partially or totally treated in another institution, who received chemotherapy for another malignancy, with metastatic disease at the time of diagnosis, or who were operated at baseline without receiving first chemoradiation treatment. Patients with incomplete data on clinical stage or systemic treatment were also excluded. This resulted in a population of 183 patients **(Figure 1)**. All patients in the study population were sampled, and the sampling was non-probabilistic.

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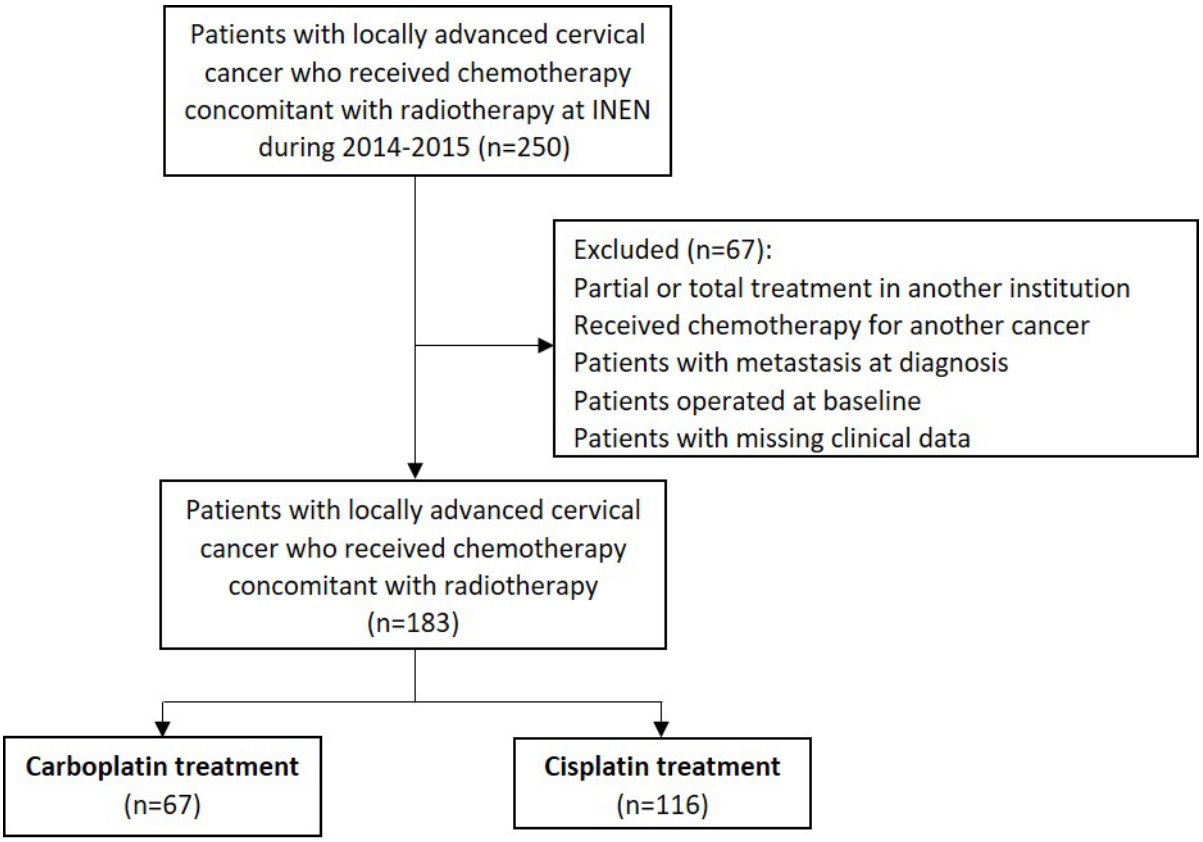
Figure 1: Flow diagram of the included patients who were analyzed



Definition of variables

Quantitative variables consisted of age at diagnosis, treatment duration, and quantity of cycle treatment. Qualitative variables were formed by clinical stages, tumor histology, platinum-based treatment, BT, patient survival status, response to treatment and presence, type of toxicity, and toxicity grade.

Patients with topographic diagnosis C53 of the ICD10 were identified based on the list provided by the Department of Statistics and Epidemiology. Clinical staging at diagnosis was performed according to the FIGO classification from 2009, most recently during the 2014-2015 period (Pecorelli, Zigliani, and Odicino 2009). After that, we selected patients with LACC who received chemoradiation treatment. Patients underwent complete external beam radiotherapy (40–45 Gy) to the pelvic region with weekly sessions of cisplatin (40 mg/m2) or carboplatin (AUC2), followed by high-dose intracavitary brachytherapy (Lanciano et al. 2005; Singh et al. 2013).

Treatment-related adverse events were analyzed during the treatment period up to 28 days after the last treatment and scored according to the Common Terminology Criteria for Adverse Events from the National Institute of Cancer (NCI-CTCAE) version 4.0 (National Institutes of Health and National Cancer Institute 2009). Complete response was defined as the total disappearance of all clinically detectable disease. Partial response was understood as a reduction greater or equal to 50% in tumor size. We considered progressive disease as the increase in the volume of the tumor or the appearance of new lesions (T. Hu et al. 2012) Progression-free Survival (PFS) was calculated from the surgery date to the malignancy progression. Overall Survival (OS) was calculated from the surgery date to death from any cause.

Data collection

Medical records were reviewed to collect clinical data, treatment characteristics, adverse events (AEs), local tumor response, and survival-related information. The present study collected clinical data about the patients, including their age at diagnosis, clinical stage, and histology; treatment characterization such as chemotherapy type (carboplatin or cisplatin), number of

cycles, beginning and end of treatment, BT use and response to treatment at tumor level, progression status, and survival status. We registered the information and created a database with Microsoft Excel 2000 (Microsoft Corporation, USA) to allow cross-referencing and exportation to statistical programs.

Statistical analysis

Categorical variables were evaluated with the chi-square test or Fisher's exact test, as appropriate, and displayed as frequencies and percentages. Continuous variables were analyzed using the Wilcoxon test and expressed as the median with the interquartile range. Kaplan-Meier curves were obtained to evaluate the effect of carboplatin vs. cisplatin on PFS and OS. In addition, a univariate Cox proportional hazards model was used to identify risk factors associated with PFS and OS. All statistical analyses were performed using RSoftware version 4.03, packages "survival", "survminer" and "getsummary". A threshold of statistical significance of $p \leq 0.05$ was established for all tests.

Limitations and feasibility

The study is feasible since INEN is a national reference and research entity. Therefore, the study included patients from different regions in Peru. The retrospective approach allows for a distinctive separation and comparison between treatments.

The limitations include the possibility of information loss in the clinical records or inadequate data registration. The study also severely depends on how consistently the patients attend their medical appointments. This could have affected the registration of AEs and the follow-up time for evaluating survival outcomes. To mitigate limitations, we employed statistical methods that account for missing data or incomplete records.

Ethical considerations

This study was approved by the Ethics Review Board at INEN and complied with all relevant ethical guidelines. Informed consent was not required from each patient since the retrospective approach involved no risk to their identities. Confidentiality was respected for every stage of the study.

Data availability statement

The datasets generated and analyzed during the current study are available to the corresponding author upon reasonable request.

RESULTS

Clinical and treatment characteristics

A total of 183 LACC patients who received chemoradiation as their initial treatment were included. Among these patients, 36.61% (n=67) received carboplatin, while 63.39% (n=116) were treated with cisplatin. In the general population, 180 patients received five cycles, two received three cycles, and only one had a single cycle. Patients received BT in 98.9% of cases (n=180). The median age of the overall population was 50 (Interquartile range: 44, 58) years, with the most frequent age group being 45-59 for both carboplatin and cisplatin treatments (55.2% and 54.3%, respectively, p=0.2, Table 1). An even distribution was found among treatments considering patients younger than 50 (47.8% and 54.3%, respectively, p=0.4, Table 1).

Regarding clinical stage, LACC patients were predominantly stage IIB (63.9%, n=117), with both treatments having a significantly different distribution (p=0.002). Both treatments followed the same pattern: clinical stage IIB was predominant, followed by IIIC, then IIB, and lastly, IIA. However, while clinical stage IIB was present at a similar rate for carboplatin and cisplatin treatment (64.2% and 63.8%, respectively), clinical stages IIIC and IIIB were the most different between treatments. In the carboplatin group, both frequencies were similar (19.4% and 16.4%, respectively) whereas, in the cisplatin group, 31.9% were IIIC and 2.6%, IIIB (Table 1). Histology showed no significant differences between treatment groups (p=0.3). However, there was a predominance of the squamous cell carcinoma type in all groups (86.6% and 91.4%, respectively, 164 cases in total) compared to the adenocarcinoma type (Table 1).

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Table 1: Clinicopathological characteristics according to treatment

General characteristics		N	Total, N = 1831	Carboplatin, N = 671	Cisplatin, N = 1161	p-value2
Clinical characteristics	Age (years)	183	50 (44, 58)	51 (45, 59)	50 (43, 56)	0.2
	Age group (years) ≤ 50 > 50	183	 95 (51.9%) 88 (48.1%)	 32 (47.8%) 35 (52.2%)	 63 (54.3%) 53 (45.7%)	0.4
	Age group (years) ≤ 44 45 - 59 60 - 74 ≥ 75	183	 50 (27.3%) 100 (54.6%) 29 (15.8%) 4 (2.2%)	 14 (20.9%) 37 (55.2%) 13 (19.4%) 3 (4.5%)	 36 (31%) 63 (54.3%) 16 (13.8%) 1 (0.9%)	0.2
	Clinical stages IIA IIB IIIB IIIC	183	 2 (1.1%) 117 (63.9%) 14 (7.7%) 50 (27.3%)	 0 (0%) 43 (64.2%) 11 (16.4%) 13 (19.4%)	 2 (1.7%) 74 (63.8%) 3 (2.6%) 37 (31.9%)	0.002
	Histology Adenocarcinoma Squamous cell carcinoma	183	 19 (10.4%) 164 (89.6%)	 9 (13.4%) 58 (86.6%)	 10 (8.6%) 106 (91.4%)	0.3
Treatment characteristics	**Cycles** 1 3 5	183	 1 (0.5%) 2 (1.1%) 180 (98%)	 1 (1.5%) 1 (1.5%) 65 (97%)	 0 (0%) 1 (0.9%) 115 (99%)	0.5
	Tomography evaluation No Yes	183	 165 (90%) 18 (9.8%)	 64 (96%) 3 (4.5%)	 101 (87%) 15 (13%)	0.064
	Biopsy evaluation No Yes	183	 162 (89%) 21 (11%)	 59 (88%) 8 (12%)	 103 (89%) 13 (11%)	0.9
	Treatment response Persistent disease Complete response Partial response NR	176	 31 (17.6%) 141 (80.1%) 4 (2.3%) 7	 11 (17.7%) 48 (77.4%) 3 (4.8%) 5	 20 (17.5%) 93 (81.6%) 1 (0.9%) 2	0.3
	Brachytherapy No Yes NR	182	 2 (1.1%) 180 (99%) 1	 2 (3.0%) 64 (97%) 1	 0 (0%) 116 (100%) 0	0.13

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Response	**Toxicity** No Yes	183	 43 (23.5%) 140 (76.5%)	 17 (25.4%) 50 (74.6.%)	 26 (22.4%) 90 (77.6%)	0.6
	Patient status Decease Alive	183	 28 (15.3%) 155 (84.7%)	 10 (14.9%) 57 (85.1%)	 18 (15.5%) 98 (84.5%)	>0.9
	Progression status Yes No NR	171	 115 (67.3%) 56 (32.7%) 12	 35 (60.3%) 23 (39.7%) 9	 80 (70.8%) 33 (29.2%) 3	0.2

1 Median (IQR); n (%)

2 Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Adverse events according to treatment

Out of 183 patients, only 23.5% (n=43) experienced no toxicity. Of the 67 patients receiving carboplatin, 74.6% had adverse effects compared to 77.6% of patients receiving cisplatin (p=0.6, Table 1). Anemia was the most common AE, followed by neutropenia, diarrhea, and emesis. Radiodermatitis, thrombocytopenia, and hepatotoxicity were also reported, but in much less frequency (Table 2). There was no difference in AEs between treatments; only neutropenia was lower in the carboplatin group (18% vs 41%, p=0.001, Table 2).

Table 2: Adverse events per treatment

Adverse events	N	Total, N = 1831	Carboplatin, N = 671	Cisplatin, N = 1161	p-value2
Anemia No Yes NR	178	 101 (57%) 77 (43%) 5	 35 (52%) 32 (48%) 0	 66 (59%) 45 (41%) 5	0.3
Neutropenia No Yes NR	176	 119 (68%) 57 (32%) 7	 55 (82%) 12 (18%) 0	 64 (59%) 45 (41%) 7	0.001
Thrombocytopenia No Yes NR	174	 157 (90%) 17 (9.8%) 9	 58 (87%) 9 (13%) 0	 99 (93%) 8 (7.5%) 9	0.2
Hepatotoxicity No Yes	183	 180 (98%) 3 (1.6%)	 65 (97%) 2 (3.0%)	 115 (99%) 1 (0.9%)	0.6
Diarrhea No Yes NR	175	 123 (70%) 52 (30%) 8	 52 (78%) 15 (22%) 0	 71 (66%) 37 (34%) 8	0.095

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Emesis No Yes NR	175	125 (71%) 50 (29%) 8	52 (78%) 15 (22%) 0	73 (68%) 35 (32%) 8	0.2
Radiodermatitis No Yes	183	157 (86%) 26 (14%)	54 (81%) 13 (19%)	103 (89%) 13 (11%)	0.13
1 n (%) 2 Pearson's Chi-squared test; Fisher's exact test					

Association between treatment and response

Treatment response was evaluated in 176 patients of 183 total (7 cases of missing data). In our study, 77.4% (n=48) and 81.6% (n=93) of carboplatin- and cisplatin-treated patients achieved pCR, respectively (Table 1). Neither pCR, persistence to treatment, nor partial response showed differences between treatments (p=0.3, Table 1).

Progression was found in 67.3% (n=115, out of 171 patients total, with 12 cases of missing data), 60.3% in the carboplatin group patients had disease progression vs. 70.8% of cisplatin-treated patients (p=0.2, Table 1).

Association to Survival Outcomes

At the time of analysis, 84.7% (n=155) of all 183 patients were alive; 85.1% (n=57) and 84.5% (n=98) carboplatin- and cisplatin-treated patients, respectively (p>0.9, Table 1).

At a 5-year follow-up, OS is not significantly different between treatments (p=0.41, Figure 2A), but PFS seems more favorable in the cisplatin group (p=0.048, Figure 2B). However, Cox analysis did not show a significant improvement in OS (HR=0.72, 95% CI=0.33-1.57, p=0.4, Table 3) nor PFS (HR=0.59, 95% CI=0.34-1.00, p=0.055, Table 3).

It was observed that those who achieved a complete response had better survival compared to those with persistent disease (OS: HR=0.15, 95% CI=0.06-0.38, p<0.001. PFS: HR=0.08, 95% CI=0.04-0.14, p<0.001, Table 3).

It was also observed that oldness was associated with OS (age: HR=1.05, 95% CI=1.01-1.09, p=0.008. AGE>50: HR=2.34, 95% CI=1.08-5.07, p=0.028, Table 3), but not PFS. Likewise, histology, platinum-based treatment type, and toxicity presence were not associated with survival (Table 3).

Table 3: Cox analysis for survival outcomes

General characteristics		Overall Survival				Progression-free Survival			
		N	HR1	IC 95%1	p-value	N	HR1	IC 95%1	p-value
Clinical characteristics	Age (years)	183	1.05	1.01, 1.09	0.008	170	1.02	1.00, 1.05	0.1
	Age group (years) ≤ 50 > 50	183	 — 2.34	 — 1.08, 5.07	0.028	170	 — 1.53	 — 0.90, 2.60	0.12
	Age group (years) ≤ 44 45 - 59 60 - 74 ≥ 75	183	 — 2.25 3.8 4.26	 — 0.75, 6.73 1.11, 13.0 0.47, 38.7	0.15	170	 — 1.28 1.82 1.41	 — 0.67, 2.45 0.82, 4.06 0.18, 10.8	0.6
	Histology Adenocarcinoma Squamous cell carcinoma	183	 — 0.41	 — 0.17, 1.01	0.076	170	 — 0.5	 — 0.25, 1.03	0.082

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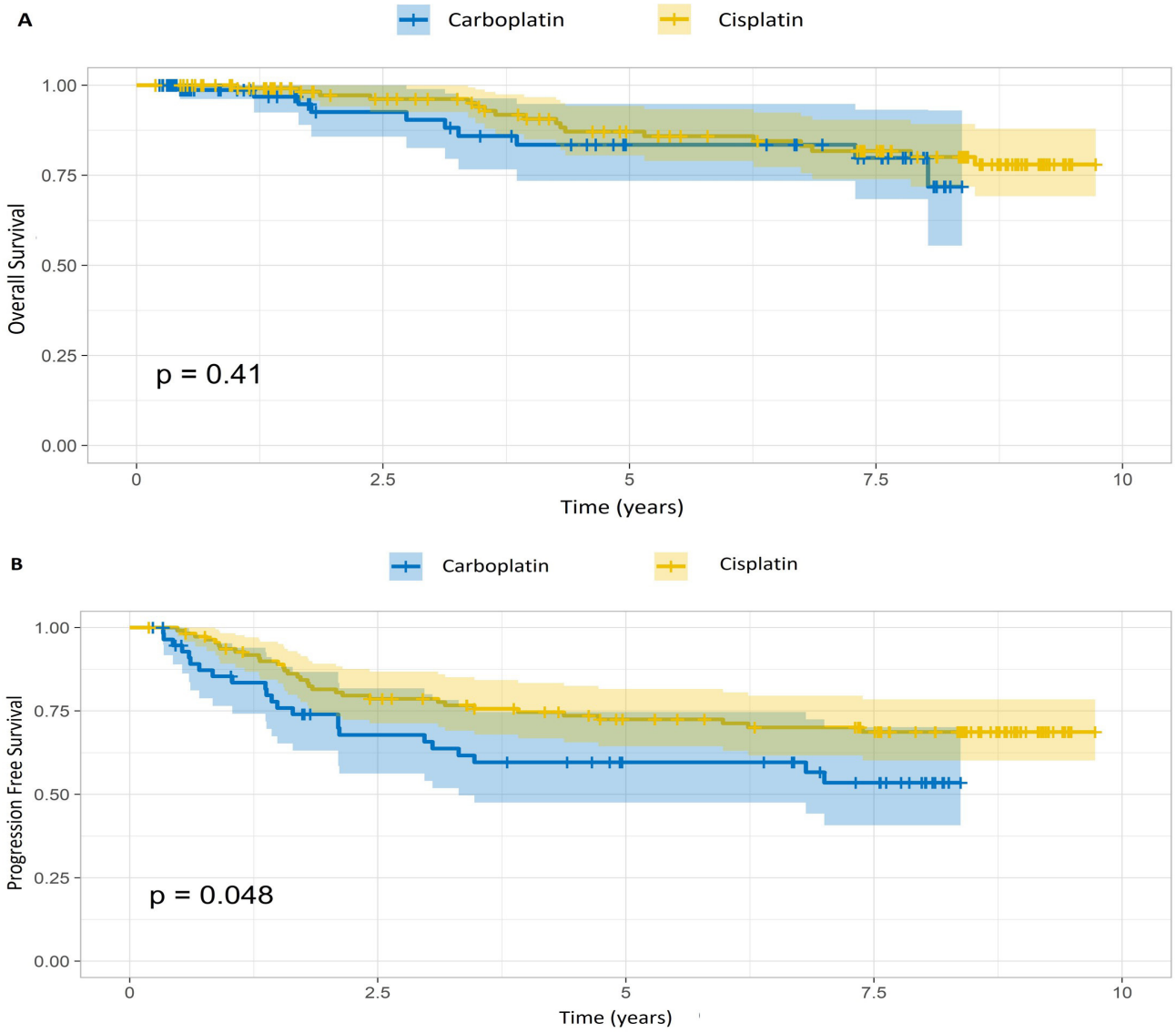
Treatment characteristics	**Platinum-based teatment** Carboplatin Cisplatin	183	— 0.72	— 0.33, 1.57	0.4	170	— 0.59	— 0.34, 1.00	0.055
	Treatment response Persistent disease Complete response Partial response	176	— 0.15 0.96	— 0.06, 0.38 0.20, 4.66	<0.001	165	— 0.08 0.31	— 0.04, 0.14 0.07, 1.32	<0.001
Respuesta	**Toxicidad** No Yes	183	— 2.2	— 0.66, 7.29	0.2	170	— 0.97	— 0.51, 1.84	>0.9

Figure 2: Survival outcomes according to treatment. A: OS and B: PFS



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DISCUSSION

We found out that LACC patients were mostly likely to be between the ages of 45 and 59, with a median age of 50. The predominant histology and clinical stage of LACC patients was squamous cell carcinoma, with IIB stage being the predominant histology and clinical stage, respectively.

The age group distribution in LACC patients seems to follow a similar pattern to CC frequencies recorded during the same period in the Lima Metropolitan Registry, with the 45-59 age group being the highest, followed by women under 44 (Payet Meza et al. 2021). Median age and age distribution are also in accordance with previous LACC studies, around 50. (Sanz-Garcia et al. 2014; Gennigens et al. 2021; Moore et al. 2016)

It is necessary to mention that our youngest patient was 28 years old at diagnosis, and we joined patients 44 and under in the same group. Meanwhile, the previous registry accounted for cases in underage girls and made a distinction for cases from 15-29 years and 30-44 years. This slight difference may be explained by earlier detection in the former group since the disease is unlikely to have extended to pelvic-adjacent areas. And since cervical cancer is rare in women under 25 years of age (Gravdal et al. 2021), older age is associated with increased odds of diagnosis at an advanced stage (OR: 1.03, 95% CI: 1.01–1.05) (Ibrahim et al. 2011).

Squamous cell carcinoma, being the primary histology over adenocarcinoma (89.6% vs 10.4%), is also to be expected. From 2013-2015, it was the most common CC histologic type in Lima (Payet Meza et al. 2021) and it was present in 70%-88% of LACC patients(Sanz-Garcia et al. 2014; Gravdal et al. 2021; Moore et al. 2016; Marth et al. 2017; Santos et al. 2001; Gennigens et al. 2021; Cetina et al. 2008).

Regarding the clinical stage, IIB has the highest frequency. This agrees with other studies, where said frequency varies between 48%-55% (Sanz-Garcia et al. 2014; Moore et al. 2016; Katanyoo et al. 2011; Cetina et al. 2008). However, in those studies, as in ours, stage IIB is followed by IIIB instead of IIIC. The lower screening rates and higher CC incidence in lower income settings (Payet Meza et al. 2021; Aguilar et al. 2016), as well as the tendency showed by Andean Peruvian women to wait until they experience more severe symptoms to seek a diagnosis/treatment (Luque et al. 2016) may cover this difference.

The preferred treatment could be one factor to consider about the high mortality rate. The standard of care (SOC) for LACC is cisplatin-based chemoradiotherapy plus BT, given its superiority over radiotherapy alone and NAC plus surgery in regards to DFS and OS (Korenaga et al. 2022; Gennigens et al. 2021; Marth et al. 2017; Gaducci and Cosio 2020; Bhatla et al. 2021; Cibula et al. 2018). This treatment, although highly effective, is associated with several adverse events that can lead to an incomplete regimen, which in turn is associated with higher recurrence (locoregional failure HR 3.02, 95% CI 1.08-8.45, p=0.03; distant failure HR 2.71, 95% CI 1.13-6.47, p=0.02) and worse survival (OS HR 4.91, 95% CI 1.27-18.98, p=0.02) (Kotha et al. 2022). How much the cisplatin incomplete treatment weights upon mortality rate may need further research, especially in the Peruvian population where other factors such as economy, geography, fear, and lack of knowledge/conscience have a great impact on patients seeking and adhering to treatment (Payet Meza et al. 2021; Aguilar et al. 2016).

That nearly all of our patients received BT for five cycles (98.6%) is relevant to the study because, as part of SOC, patients who received BT had shown better OS (Alimena et al. 2019; Korenaga et al. 2022). Similarly, BT completion within eight weeks is associated with a significantly higher OS than receiving BT for more time (131.0 months vs 95.5 months, p<0.0001) and not receiving at all (49.2-78.1 months, p<0.0001) (Korenaga et al. 2022). Only two patients (3.0%) did not receive BT in the carboplatin group meanwhile everyone did in the cisplatin group. Since their difference was insignificant (p=0.13), BT efficiency may not differ regardless of the platinum-based treatment, as BT plus carboplatin has been shown to work adequately (Landrum et al. 2010). This is further accepted when acknowledging the equivalence in almost all of the AEs and survival outcomes in our results. However, comparing cisplatin- and carboplatin-based treatments focused solely on BT may require more research to clarify any specific influence.

Among our patients, 36.61% (n=67) received carboplatin, while 63.39% (n=116) were treated with cisplatin. Whether this was due to patient preference or medical protocol was not determined. That most patients received cisplatin treatment is not surprising due to being part of international guidelines recommendations (Bhatla et al. 2021; Cibula et al. 2018). While most studies that compare both treatments had a smaller or similar sample size for the carboplatin group (Tharavichitkul et al. 2016; Sebastião et al. 2016; Nam et al. 2013; Au-Yeung et al. 2013), some more recent retrospective studies indicated a slightly wider use of carboplatin with no statistical difference in OS (Sama et al. 2023; Richters, Boormans, et al. 2022). It must be noted that in those studies, the carboplatin groups tended to have older patients with poor performance status and renal function. Although both studies were not done in patients with CC, limited-stage small-cell lung cancer (Sama et

al. 2023), and metastatic urothelial carcinoma of the bladder (Richters, Boormans, et al. 2022), the absence of a statistically significant difference is noteworthy and may suggest an increasing preference for carboplatin.

While both treatments showed similar toxicity rates, with around a quarter of each group not showing any AEs (25.4% and 22.4% for carboplatin and cisplatin, respectively, p=0.6), the AEs were similar in rates, too. The most common AE was anemia, followed by neutropenia and diarrhea. Our population showed AEs registered before in cisplatin. Previous studies have shown that cisplatin has had high rates of adequate response (Nam et al. 2013; Rose et al. 1999; Lanciano et al. 2005), but often linked to elevated hematological toxicity (such as thrombocytopenia, anemia, neutropenia, lymphopenia), nephrotoxicity, gastrointestinal problems, hepatotoxicity and pulmonary and cardiovascular toxicities too (Moore et al. 2016; Miller et al. 2010; Rose et al. 1999; Buda et al. 2005; Lissoni et al. 2009). On the other hand, carboplatin has less severe AEs (especially in regards to hematological and gastrointestinal toxicities) (Katanyoo et al. 2011; Kitagawa et al. 2015; Tharavichitkul et al. 2016; S. Hu et al. 2023). Carboplatin has also achieved a complete response with a low chance of recurrence and adequate-to-comparable survival outcomes (Katanyoo et al. 2011; Cetina et al. 2008). This could lead to better patient compliance with carboplatin than with cisplatin since it has been highlighted that incomplete treatment with cisplatin is usually due to low tolerance, high AEs, and resistance (Kotha et al. 2022). Which in turn increases the likelihood of progression and cancer-related death. Noteworthily, nephrotoxicity is considered a dose-limitant for cisplatin and has shown in greater rates compared to carboplatin (Miller et al. 2010; Tharavichitkul et al. 2016), however it did not appear as a common AE in our patients. Only neutropenia frequency was statistically different and lower in the carboplatin group (18% vs. 41%, p=0.001); this is in accordance with cisplatin producing higher grade neutropenia (Tharavichitkul et al. 2016; Gaducci and Cosio 2020). However, another study puts neutropenia as the main hematological toxicity for carboplatin (Singh et al. 2013), and another compares it to a paclitaxel plus ifosfamide plus cisplatin regimen resulting in a better hematological toxicity profile (Salihi et al. 2017). These discrepancies are relevant because both use weekly paclitaxel-carboplatin and need further inspection.

However, it remains significant that, for our population, the AEs are equivalent between treatments except neutropenia and, given that carboplatin is recommended as an alternative for patients that are not fit to receive cisplatin (Gennigens et al. 2021) and it is more commonly used in older patients with poorer performance status and renal function underscores (Sama et al. 2023; Richters, Boormans, et al. 2022), it has potential as a viable alternative in specific patient population; in delicate-state patients who not respond well with higher grades AE or in older ones. In our findings, around 18% (n=33) of patients were over 60, and 2% (n=4) were over 75 years. In general, the older patients had a higher risk of death (age>50: HR=2.34, 95% CI=1.08-5.07, p=0.028), supported by Moore et al 2016, where after 50, the risk increase is 2% (HR 1.02; 95% CI, 1.01–1.04) for every 1-year increase in age in LACC patients). Although that was done in a multivariable analysis, where other variables are not constant, disease-related mortality is not significant (Moore et al. 2016). Regardless, patients with other health problems that could benefit from carboplatin were not specified in the data collection, but there is evidence for better patient performance (Fong et al. 2014; Cetina et al. 2008).

Our results show no difference in survival outcomes between treatments. However, a dissonance was found in PFS, favoring cisplatin. Kaplan-Meier analysis suggested that the mortality was higher for carboplatin and significant (p=0.048), but not in the Cox analysis (p=0.055).

This incongruence could be explained by limitations in the Kaplan-Meier analysis; the log-rank test does not provide an estimate of the size difference between the groups and its related confidence interval (Bland and Altman 2004), nor does it adjust for potential confounders, unlike the Cox proportional hazard regression model (Spruance et al. 2004; Barraclough, Simms, and Govindan 2011).

Our findings showed similar responses (persistence, partial, and complete response) and progression rates (p=0.3, p=0.2). Likewise, OS and PFS are similar. Suggesting that both treatments are equivalent in efficacy. We see this is also found in other studies where survival outcomes and recurrences are not statistically different (Nam et al. 2013; Kitagawa et al. 2015; Katanyoo et al. 2011; Xue et al. 2018; Tharavichitkul et al. 2016; Sebastião et al. 2016), even in other carcinomas (Richters, Kiemeney, et al. 2022; Richters, Boormans, et al. 2022; Sama et al. 2023). Also, in our results, neither histology was associated with either OS or DFS. This is peculiar since most studies agree that patients with squamous cell carcinoma tend to have higher OS (Marth et al. 2017). The discrepancy may be related to the small sample size, particularly adenocarcinoma, which may have limited the relevance of our findings. Regardless, it adds to the current controversy about whether the histological type is prognostic to survival. (Marth et al. 2017; Korenaga et al. 2022).

CONCLUSION

In summary, cisplatin and carboplatin showed similar survival outcomes and safety profiles. Carboplatin stood out only in its more favorable tolerance towards neutropenia. These findings underscore the importance of considering both efficacy and tolerability when choosing the appropriate therapy for patients with locally advanced cervical cancer and suggest that carboplatin could be a valid alternative for patients with a more delicate clinical condition who might face challenges with cisplatin-associated toxicity.

Authors contributions

Conception and design: NV, IO, LCJ. Administrative support: IO, NHC. Data collection and assembly: IO, LCJ. Data analysis and interpretation: IO, NHC, YF. Manuscript writing: NHC. Final approval of manuscript: All authors. Accountable for all aspects of the work: All authors. All authors contributed to the article and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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