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Disease Free Survival and Overall Survival in Triple-Negative Breast Cancer Patients with Post-Neoadjuvant Residual Disease Treated with Adjuvant Capecitabine

Capecitabine in breast cancer

Supervivencia libre de progresión y supervivencia global en pacientes con cáncer de mama triple negativo con enfermedad residual postneoadyuvancia tratadas con capecitabina adyuvante

Capecitabina en cáncer de mama

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ABSTRACT
Background: The scarcity of effective therapies has contributed to poor outcomes in triple-negative breast cancer. **Objective:** To evaluate overall and progression-free survival in patients with triple-negative breast cancer with post-neoadjuvant residual disease, treated with Capecitabine. **Methods:** Retrospective cohort study. Kaplan-Meier survival functions were calculated. Additionally, Cox regression models were developed for association analysis. **Results:** Forty-one patients were included, of whom 25 (61%) were postmenopausal, 23 (56.1%) had initial tumors ≥5.1cm. The median PFS was 25.03 months (95% CI, 13.37 - 36.68). Twenty six percent of patients had progression at 36 months follow-up, 54.5% of those who had progression were premenopausal. In women with postmenopausal status, higher PFS was observed (HR0.32, 95% CI 0.09 -0.98, p 0.045). The median OS was 55.60 months (95% CI, 46.5-58.5). There was no significant difference between the RCB (Residual Cancer Burden) score and PFS and OS. **Conclusion:** favorable results were observed in patients with post-neoadjuvant residual disease treated with adjuvant Capecitabine, particularly in postmenopausal patients with less previous tumor size.

Keywords: Triple-negative breast cancer, Capecitabine, ARB, residual disease, disease free survival, overall survival.

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RESUMEN

Antecedentes: La escasez de terapias eficaces ha contribuido a que el cáncer de mama triple negativo tenga resultados desfavorables. **Objetivo:** Evaluar la supervivencia global y libre de progresión en pacientes con cáncer de mama triple negativo con enfermedad residual postneoadyuvancia, tratadas con capecitabina. **Métodos:** Estudio de cohorte retrospectiva. Se calcularon funciones de supervivencia de Kaplan-Meier. Además, se desarrollaron modelos de regresión de Cox para análisis de asociación. **Resultados:** Se incluyeron 41 pacientes, de las cuales 25 (61 %) eran posmenopáusicas y 23 (56,1 %) tenían tumores iniciales ≥ 5,1 cm. La mediana de supervivencia libre de progresión fue de 25,03 meses (IC 95 %, 13,37-36,68). El 26,8 % de las pacientes presentaron progresión a los 36 meses de seguimiento, entre ellas, el 54,5 % eran premenopáusicas. En las mujeres con estado postmenopáusico se observó mayor supervivencia libre de progresión (HR 0,32, IC95 % 0,09-0,98, p 0,045). La mediana de supervivencia global fue de 55,60 meses (IC 95 %, 46,5-58,5). No se observaron diferencias significativas entre el score RCB (Residual Cancer Burden) y la supervivencia libre de progresión y la supervivencia global. **Conclusión:** En pacientes con enfermedad residual postneoadyuvancia tratadas con capecitabina adyuvante se observaron resultados favorables, sobre todo en aquellas pacientes postmenopáusicas y con menor tamaño tumoral previo.

Palabras Clave: Cáncer de mama triple negativo, capecitabina RCB, enfermedad residual, supervivencia libre de progresión, supervivencia global.

1. Introduction

Breast cancer is the most common cancer and specific cause of death among women living in Latin America and Caribbean region with 200,000 new cases and more than 52,000 deaths per year (1). It is also located in the first place of incidence for Colombia with 15,509 cases and a mortality of 4,411 cases by 2020 (2). Among all new cases of breast cancer, triple negative breast cancer (TNBC) occurs at a frequency from 15% to 20% (3).

The high heterogeneity, aggressiveness and absence of a receptor that acts as a target for the development of new drugs explain the fact that TNBC is the subtype with the least favorable clinical results and with the smallest number of effective therapeutic options (3).

Although some inhibitors have proven to be effective in the neoadjuvant phase, their high price and not very good cost-effectiveness mean that from the perspective of payers, these inhibitors at their current price will probably not be the choice for patients with TNBC (4). This is why chemotherapy continues to be the cornerstone of treatment, both neoadjuvant and adjuvant. In the neoadjuvant setting, chemotherapy is typically administered with the goal of shrinking the tumor and potentially achieving a better surgical outcome, as well as evaluating the patient's prognosis (5). Currently, the standard chemotherapy for the treatment of TNBC is represented by the sequence of taxanes (docetaxel/paclitaxel) and anthracycline (6-10).

However, even though the chemotherapy regimen is effective, the 10-year risk of relapse of TNBC ranges between 20 and - 40% (11); therefore, it is necessary to explore the role of new chemotherapy agents and regimens to obtain important benefits in the survival of these patients.

Capecitabine is a nucleoside analogue —commonly used in patients with metastatic breast cancer —whose role in the treatment of TNBC has aroused special interest (11,12).

Several studies have analyzed the role of Capecitabine in the treatment of TNBC and obtained heterogeneous results. The CREATE-X study evaluated the role of Capecitabine in relation to DFS in patients with triple negative disease, the DFS rate was 69.8% in the Capecitabine group versus 56.1% in the control group (HR 0 .58; 95% CI, 0.39 to 0.87), and the OS rate was 78.8% versus 70.3% (hazard ratio for death, 0.52; 95% CI, 0.30 to 0.90) (13). The GEICAM/2003-11-CIBOMA/2004-01 study explored adjuvant Capecitabine after standard chemotherapy in patients with early TNBC, but this study failed to show a statistically significant increase in DFS when adding Capecitabine to standard chemotherapy in patients with early TNBC (14).

Considering the contradictory results and the absence of data from Latin American populations on the effect of neoadjuvant Capecitabine in patients with TNBC, it is necessary to provide new evidence that allows drawing conclusions and individualizing treatment options for these patients.

The primary objective of this study was to evaluate the progression-free survival (PFS) of patients with stage I-III triple-negative breast cancer with postneoadjuvant residual disease, treated with Capecitabine,

in an oncology reference center in the city of Medellín. As a secondary objective, overall survival (OS) was evaluated in these patients.

2. Materials and methods

The protocol of this study was approved by the institutional ethics committee for research in human beings of the CES University (cod. Acta211Proy973) and by Fundación Colombiana de Cancerología Clínica Vida (FCCCV). Since this is a retrospective study, without any intervention in the care of the patients, the informed consent used for research studies at the institution was not required. Patient data were guaranteed to be submitted anonymously and confidentially. The reporting of results follows the recommendations of the STROBE guideline (15).

2.1. Design and context

Observational follow-up study of a cohort from April 15, 2018 to April 27, 2023, until death or administrative censorship, based on records taken from the database of the Fundación Colombiana de Cancerología Clínica Vida (FCCCV) of Medellín between 2019 and 2023. Data collection was carried out from February 15, 2023 to May 18, 2023; mortality of all patients was evaluated on June 6, 2023 on the Adres platform (16). The Administrator of the Resources of the General Social Security Health System (ADRES by its Spanish acronym) is the State entity in which the population's records are located, including their date of death.

2.2. Participants

From the information provided by the FCCCV, a total of 144 records of patients who were prescribed Capecitabine at the institution were reviewed. Patients were included in the study if they met the following criteria: women over 18 years of age, with triple negative breast cancer, stage I–III, with residual disease after neoadjuvant chemotherapy, and who received Capecitabine as adjuvant monotherapy. The exclusion criteria were bilateral breast cancer, multiple synchronous cancers, previous treatment with oral Fluoracil, pregnant and lactating patients. Patients whose records had more than 10% of missing data were also excluded.

2.3. Triple negative breast cancer

The triple negative subtype was defined as hormone receptor negativity by immunohistochemistry and Her2 negative by immunohistochemistry (Her2 0 or 1+) or FISH (*in situ* hybridization) test in cases of equivocal Her2 (2+).

2.4. Variables

The primary outcome variable was OS, which was calculated from the time of treatment initiation to the last follow-up or time of death from any cause. PFS was a secondary outcome variable that was calculated from the time of treatment initiation until progression was documented or to the last follow-up without evidence of progression. The initial characteristics of the patients were considered; age, menopausal status, tumor size, axillary lymph node involvement, neoadjuvant chemotherapy regimen received, surgery performed, as well as characteristics of residual disease focused on Residual Tumor Burden (RCB).

2.5. Data sources

The FCCCV IT team was asked for the list of patients admitted between 2019 to 2023 for TNBC, treated with adjuvant Capecitabine, subsequently a review of the medical history of each patient was carried out to determine who met the inclusion criteria and thus obtain the data of interest for the study.

To determine the diagnosis, the date of the first histopathological study was taken. For progression, the date of the first imaging study that showed locoregional or distant change was recorded. Finally, the cut-off date to evaluate survival was June 6, 2023, for all patients by checking their activity status on the Adres platform (16).

2.6. Bias control

Data collection was carried out by a researcher who verified in each clinical record that the inclusion requirements were met and entered them in the corresponding Excel template where each variable of interest was stipulated. In case of doubt about any variable record, it was consulted with expert researchers in the area (mastologist, oncologist or epidemiologist).

The clinical record was initially reviewed, if it lacked information or was incomplete, the mastology evaluations were verified and in cases in which none was available, the data were extracted from the notes of the other specialties related to breast care of the patient due to their oncological condition (pain and palliative care or oncological rehabilitation).

2.7. Statistical methods

A univariate analysis was performed to characterize the study population considering the nature of the variables. In the case of quantitative variables, the Kolmogorov-Smirnov normality test was performed to define whether they presented averages or medians. Qualitative variables were analyzed using absolute and relative frequencies. Median survival was calculated using the Kaplan Meier curve.

For the bivariate analysis, differences in survival according to covariates were calculated by the log Rank test.

A multivariate analysis was performed through the association between covariates and time to event using COX regression. A p value less than 0.05 was considered statistically significant. All analyzes were performed in SPSS version 25.

3. Results

3.1. Participants

A total of 41 patients met the inclusion criteria. With a median age of 55 (44.5-65.5) years old. Of them, 25 (61%) were postmenopausal and only 16 (39%) were premenopausal. The most common histological subtype was invasive ductal carcinoma in 39 people (95.1%). T4b was the most common staging of the patients in 14 (36.6%). The initial descriptive data of the patients are presented in Table 1.

3.2. Response to neoadjuvant chemotherapy and Capecitabine

In 70% of cases, chemotherapy management consisted of the use of doxorubicin (60 mg/m2) plus cyclophosphamide (600 mg/m2) every 21 days with support of granulocyte colony-stimulating factors in each cycle, followed by Paclitaxel (80 mg/m2) weekly for 12 weeks. Only 22% received a regimen with anthracyclines in dense doses (every 14 days) due to access barriers. The use of platinum in neoadjuvant treatment was carried out in 68% of cases in conjunction with paclitaxel.

The most common neoadjuvant chemotherapy regimen was anthracyclic plus taxanes in 36 patients (87.8%), the other regimen used in 3 patients (7.3%) was taxanes plus platinum, as described in Table 1.

In eight patients (19.5%), the pathology of the surgical specimen reported RCB 1, in 20 patients (48.8%) RCB 2, and only 13 (31.7%) reported RCB 3. Table 2 shows the characteristics of the patients after neoadjuvant treatment.

Table 1. Baseline characteristics of patients with triple-negative breast cancer with postneoadjuvant residual disease

Characteristics	N (%)
Age	
Median (Interquartile Range)	55(44.5-65.5)
Menopausal status	
Premenopausal	16 (39)
Postmenopausal	25 (61)
Tumor histology	
Ductal	39 (95.1)
Lobular	1 (2.4)
Other	1 (2.4)
Tumor size at diagnosis	
≤2cm	2 (4.8)
2.1-5cm	16 (39)
≥5.1cm	23 (56.1)
Prior t	
T2	11 (26.8)
T3	14 (34.1)
T4b	15 (36.6)
T4c	1 (2.4)
Histological grade	
1	1 (2.4)
2	10 (24.4)
3	30 (76.2)
Ki67, Median (Interquartile Range)	60 (40-80)
Focality	
Unifocal	38 (92.7)
Multifocal	2 (4.9)
Multicentric	1 (2.4)
Lymph node involvement	
No	9 (31)
Yes	32 (78)
Neoadjuvant received	
Anthracyclics + Taxanes	36 (87.8)
Taxanes	1 (2.4)
Docetaxel + cyclophosphamide	1 (2.4)
Taxanes and platinum	3 (7.3)
Surgery on breast	
Conservative surgery	13 (31.7)
Mastectomy	28 (68.2)
Axillary surgery performed	
BGC	7 (17.1)
BGC + VA	1 (2.1)
GOES	27 (65.9)
Without axillary surgery	6 (14.6)
Adjuvant radiotherapy	40 (97.6)

T; tumor size (TNM), BGC; sentinel lymph node biopsy, VA; axillary emptying.

Table 2. Response to neoadjuvant chemotherapy in patients with triple-negative breast cancer with post-neoadjuvant residual disease

Characteristics	N (%)
RCB	
1	8 (19.5)
2	20 (48.8)
3	13 (31.7)
Residual tumor size (mm)	
Median (Interquartile Range)	23 (10-36)
ypt	
ypT0	1 (2,4)
ypT1a-ypT4c	40 (97.6)
Positive lymph nodes	
0	23 (56.1)
1-3	12 (29.3)
≥4	6 (16.6)
Nodal metastasis size (mm), median (IQR)	2.63 (0-3)
Tumor bed size (mm), median (IQR)	23 (11.50-38.50)
Postneoadjuvant cellularity (%), median (IQR)	50 (12.50-65)
Residual DCIS (%), median (IQR)	1 (0-20)
Progression	
No	30 (76.2)
Yes	11 (26.8)
Progression site	
Regional	2 (18.1)
Loco-regional	2 (18.1)
Distance	7 (63.6)
Remote progression site	
CNS	1 (2,4)
Lungs	2 (4.9)
Ganglion	2 (4.9)
Bones	2 (4.9)
Death	
No	37 (90.2)
Yes	4 (9.8)

RCB: Residual Cancer Burden; ypT: postneoadjuvant residual tumor size; DCIS: ductal carcinoma *in situ*; CNS: central nervous system

3.3. Progression-Free Survival

Median PFS was 25.03 months (95% CI, 13.37 – 36.68), see Figure 1. Eleven patients (26.8%) presented disease progression after starting adjuvant treatment with Capecitabine. Among the total of patients who presented progression, distant progression was documented in seven patients (63.6%), regional progression in 2 (18.1%), and loco-regional progression in 2 (18.1%), as described in Table 2. The most frequent distant progression was lymph node progression in 2 patients (2.9%), followed by metastasis to the lung and bones, both groups with the same representation of 2 patients (4.9%). Among the patients with progression, four died from this cause. When performing the multivariate analysis (Table 3), the statistically significant characteristics associated with patients who received adjuvant Capecitabine were postmenopausal status as a protective factor for progression (HR0.32, 95% CI 0.09 -0.98, p 0.045), and a larger previous size presented a greater risk of disease progression over time (HR1.69, 95% CI, 1.02-2.81, p =0.041).

Figure 1. Progression-free survival in triple-negative breast cancer patients with postneoadjuvant residual disease who received adjuvant Capecitabine

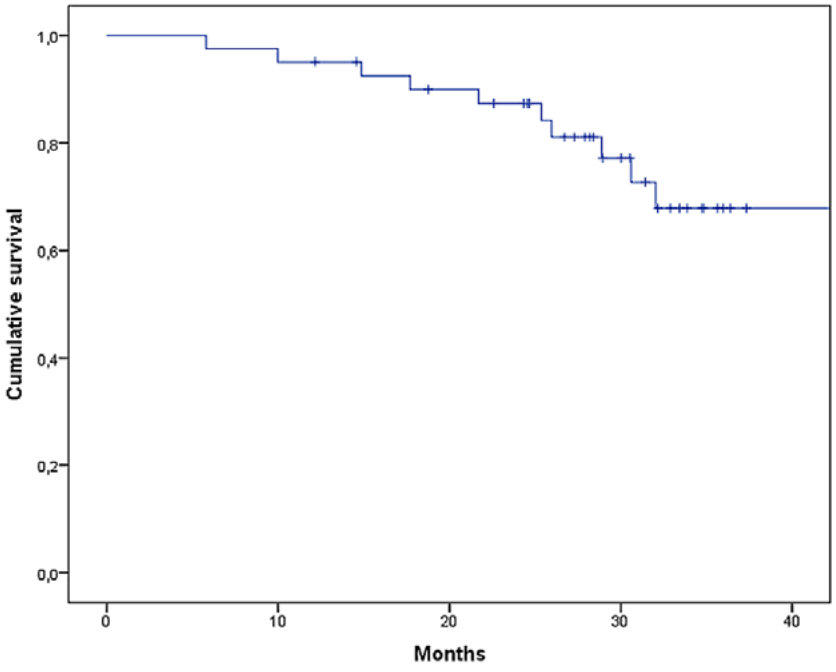


Table 3. Factors associated with time to progression in patients treated with Capecitabine

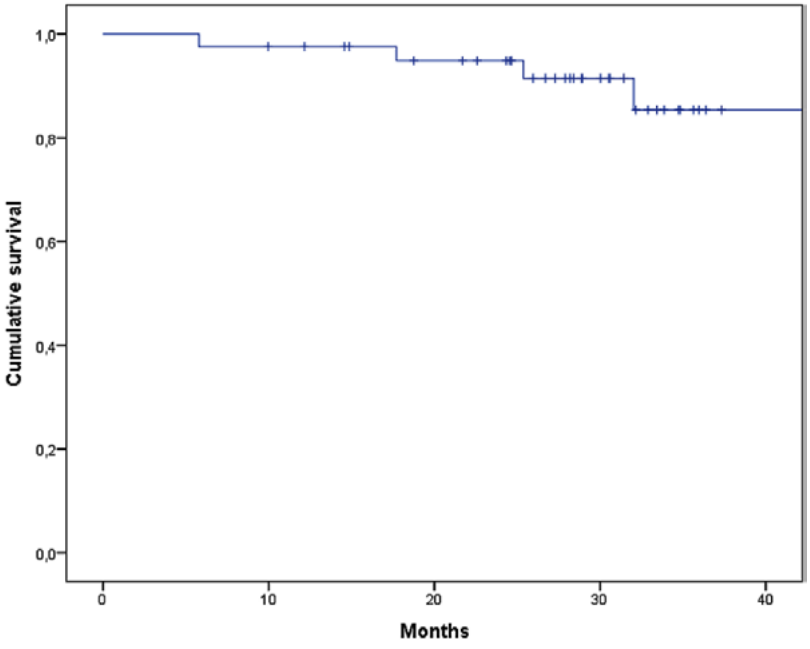
Variable	Univariate		Multivariate	
	RH 95%(CI)	p value	RH 95%(CI)	p value
Age	0.97 (0.93-1.01)	0.162		
Menopause	0.32 (0.09-0.98)	0.045		
Ki67	0.98 (0.95-1.01)	0.347		
Prior t	1.69 (1.02-2.81)	0.041	1.69 (1.02-2.81)	0.041
Previous lymph node involvement	3.02 (0.38-23.94)	0.294		
Breast surgery (mastectomy/conservative)	0.77 (0.23-2.56)	0.681		
Affected lymph nodes				
0	ref	0.039		
1 to 3	1.63 (0.36-7.38			
4	3.85 (1.10-13.39)			
Size of the largest lymph node	1.04 (0.98-1.12)	0.158		
RCB				
1	ref			
2	0.47 (0.06-3.42)	0.208		
3	1.95 (0.39-9.72)			
Focality				
Multifocal or multicentric/unifocal	0.04 (0.01-9.70)	0.854		
NACT				
(Taxanes + platinum /Anthracyclines + taxanes)	2.76 (0.71-10.61)	0.139		
YpT (ypT1a-ypT4c/Yp0)	2.13 (0.62-7.28)	0.228		

T; tumor size, BCR; Residual Cancer Burden, ypT; postneoadjuvant residual tumor size, NACT; neoadjuvant chemotherapy,

3.4. Overall survival

The mean OS was 50.37 months (95% CI, 45.3-55.5) (Figure 2). When performing the survival analysis by RCB, it was found that the mean OS was 51, 50, and 46 months for RCB 1, RCB 2, and RCB 3, respectively; this difference was not statistically significant (p = 0.614). according to the different neoadjuvant schemes or the type of surgery performed.

Figure 2. Overall survival in triple-negative breast cancer patients with postneoadjuvant residual disease who received adjuvant Capecitabine



4. Discussion

In Colombia, there is no clear characterization —retrospective or prospective— of patients with post-neoadjuvant residual disease that evaluates the possible effect of Capecitabine on the OS of the affected people. Therefore, this protocol aimed to objectively and retrospectively evaluate the characteristics of this group of patients and their behavior regarding PFS and OS. Forty-one patients were analyzed, of which 26% presented disease progression at 36 months and, out of them, four died from this cause.

The patients in this study had a median age of 55 years (IQR 44.5-65.6), similar to the Create -82 years of the patients of GEICAM/2003-11_CIBOMA/2004-01 (14). When comparing our results with those studies mentioned above, we observed that the overall survival in them was 94% at 5 years in the group that received Capecitabine (13), which is higher when compared with our study, with an OS of 80.6% at 3 years. In the GEICAM/2003-11_CIBOMA/2004-01 study, the 5-year OS in the Capecitabine group was 86.2% (13), although these results are lower. Therefore, in future prospective studies in our population, it will be necessary to evaluate what unfavorable characteristics are present. One of these characteristics could be that in our study 35.5% were tumors that affected the skin and/or chest wall, in the Create 11 CIBOMA/2004-01 no specification of that characteristic is made. Regarding tumor size, 56.1% had tumors larger than 5 cm, while in Create, in the multivariate analysis, which indicates that our cohort represents a group of patients with more aggressive initial characteristics, and therefore their prognosis would be less favorable despite the use of adjuvant Capecitabine.

In our study, 54.5% of the patients who presented progression were premenopausal. This variable was not evaluated in Create (95% CI, 0.639 - 1.176).

One of the focuses of the study was to evaluate the impact of RCB in terms of prognosis; however, we did not find statistically significant differences in both PFS and OS among groups RCB 1, RCB 2, and RCB 3. When performing the survival analysis by RCB, it was found that the mean survival was 51, 50, and 46 months for RCB 1, RCB 2, and RCB 3, respectively, and this was not statistically significant p 0.614. The Create X and GEICAM/2003-11_CIBOMA/2004-01 studies did not evaluate these variables.

In the meta-analysis carried out by Yan Li and collaborators in 2019, the efficacy of Capecitabine as adjuvant chemotherapy for early-stage TNBC treated with taxane/anthracycline-based chemotherapy was evaluated. They found a significant increase in DFS with the addition of Capecitabine (hazard ratio [HR] = 0.77, 95% CI: 0.66-0.90); a significant improvement in DFS was observed in trials involving six to eight cycles of Capecitabine addition. Furthermore, in a meta-analysis of six trials, a significant increase in overall survival was detected in the Capecitabine group (HR=0.69, 95% CI: 0.56-0.85) (17).

In the neoadjuvant treatment of TNBC, anthracyclines such as doxorubicin and epirubicin are used in dense doses in combination with cyclophosphamide. This approach, known as dose-dense chemotherapy, involves giving anthracyclines at shorter intervals than usual, for instance, every two weeks instead of every three weeks. Dose-dense chemotherapy has been shown to improve pathologic complete response rates, increase disease-free survival, and overall survival compared with standard chemotherapy in some studies (18-22). However, in our study only 22% of patients received this regimen due to barriers to access. Additionally, dose-dense chemotherapy may also be associated with a higher risk of side effects such as febrile neutropenia, which requires support with granulocytic colony factors to reduce this risk of complications (18-21).

The use of immunotherapy, and especially pembrolizumab, has been explored in the neo- and adjuvant management of triple-negative breast cancer (23). The KEYNOTE-522 study evaluated the safety and efficacy of pembrolizumab in combination with neoadjuvant chemotherapy followed by pembrolizumab as adjuvant therapy in patients with early-stage TNBC (24-25). The study included 1174 treatment-naïve patients with stage II or III TNBC and were randomly assigned to receive neoadjuvant chemotherapy with carboplatin/paclitaxel and anthracyclines with or without pembrolizumab. After surgery, patients received pembrolizumab or placebo as complementary adjuvant therapy for one year. The study showed that the addition of pembrolizumab to neoadjuvant chemotherapy increased the overall pCR rate from 51 to 65 percent independent of PD-L1 expression (24-25).

At follow-up, the addition of pembrolizumab improved 36-month DFS (85% with pembrolizumab versus 77% with placebo), with a 37% reduction in events (HR 0.63, 95% CI 0.48-0 ,82) (25). DFS with the addition of pembrolizumab had a greater absolute benefit in patients who did not achieve pCR with NACT than in patients who achieved pCR (94 versus 92 percent), thus raising the need for additional adjuvant therapy in patients with post-neoadjuvant residual disease. Capecitabine can potentially be combined with pembrolizumab in this subgroup; however, the study did not contemplate the addition of Capecitabine in these cases and we still need to wait for mature results from this long-term study in this regard. In our country, treatment with immunotherapy (pembrolizumab) is not available for use in this indication.

This study was observational, with the inherent limitations of this type of design. Results of this study enabled a comparison with international publications about the population characteristics and the benefit of treatment with Capecitabine in this group of patients. However, we found that in this group, in which OS and PFS were analyzed, results were similar to international studies. An important limitation was not having a control group to which Capecitabine was not prescribed as neoadjuvant chemotherapy.

5. Conclusions

Favorable results were observed in patients with triple-negative breast cancer with post-neoadjuvant residual disease with adjuvant Capecitabine, particularly in postmenopausal patients with smaller previous size, regardless of the RCB, since they presented better PFS and OS. More studies are needed to make a comparison between patients who received adjuvant Capecitabine and others who did not receive another regimen.

6. Abbreviations

OS: Overall Survival

PFS: Progression-free survival

RCB: residual cancer burden

TNBC: triple negative breast cancer

HR: Hazard ratio

7. Administrative information

7.1. Acknowledgment

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7.2. Authors' contribution

Arnon J. Oviedo-Tábora: Conceptualization, validation, visualization, methodology, project management, writing: review and editing. **Elsa Maria Vásquez Trespalacios:** Conceptualization, validation, visualization, methodology, project management, writing: review and editing. **Fernanda Ximena Bravo:** Conceptualization, validation, visualization, methodology, project management, writing: review and editing. **Javier Mauricio Cuello López:** Conceptualization, validation, visualization, methodology, project management, writing: review and editing. All authors read and approved the final version of the manuscript.

7.3. Financing

The study was financed with each researcher's own resources.

7.4. Statements

The protocol of this study was approved by the institutional committee of ethics of research in human beings of the CES University (cod Acta2 Ae-973) and the Fundación Colombiana de Cancerología Clínica Vida. Since this is a retrospective study without any intervention in the care of patients, consent was not required. Patient data were guaranteed to be submitted anonymously and confidentially.

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