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Effectiveness of the trastuzumab-pertuzumab dual block in neoadjuvance of HER2 positive breast cancer

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Objectives: The combination of trastuzumab and chemotherapy has been the standard neoadjuvant treatment for HER2 positive stages IIA–IIIC breast cancer. However, recent clinical trials support the neoadjuvant use of pertuzumab combined with trastuzumab in conjunction with chemotherapy to improve pathological complete response (pCR) rates. Our main objective was to determine whether the trastuzumab-pertuzumab dual blockade in neoadjuvant HER2-positive breast cancer patients achieves higher rates of pCR relative to patients where only trastuzumab was used. *Methods*: This was a prospective cohort study in patients at San Pedro's Hospital in Logroño (Spain) with HER2 positive breast cancer who were candidates for neoadjuvant therapy. 39 patients received dual block treatment and were compared with a non-concurrent (retrospective) control group of 39 patients receiving single block treatment. *Results*: According to the logit model, the coefficient that relates the probability that the pathological response is complete in the case of dual blockade was positive (2.272) and significant at 1% (*p*-value less than 0.01). The correlation coefficient between radiological and pathological response was 0.87 when we consider dual block treatment. Mucositis was the most frequent adverse effect (29.49% of the sample). There were 3 cardiac events in the single block group and none in the dual block group. *Conclusions*: The pCR was greater in the dual block group than in the single block group (69.23% versus 25.64%). There was a greater correlation between radiological and pathological response in dual blockade patients. Safety profile was similar in both groups.

Keywords

Breast neoplasms; Trastuzumab; Pertuzumab; Pathological complete response (pCR); HER-2 positive

1. Introduction

Breast cancer is the most prevalent in women worldwide, representing 30% of tumors in women [1]. Approximately 15–20% of breast cancer patients present with overexpression of the HER2 protein (human epidermal growth factor receptor 2) [2] mediated by the *HER2* gene. Cases of breast cancer with *HER2* gene amplification or HER2 protein overexpression are called HER2 positive and have been associated with an aggressive form of the disease, reduced responses to traditional therapies, and lower survival [3, 4]. The main prognostic factors in localized breast cancer are lymph node involvement and tumor size when considering high risk stage II and III tumors (tumor size >2 cm and/or lymph node involvement) [5].

Fortunately, the prognosis for HER2 positive breast cancer patients has markedly improved following the development of a number of anti-HER2 targeted therapies including trastuzumab, pertuzumab, lapatinib and trastuzumab emtansine all of them in combination with chemotherapy [4]. The clinical guidelines define HER2 positive tumors at stages IIA to IIIC as candidates for anti-HER2 neoadjuvancy [4].

In neoadjuvant treatment, the use of trastuzumab in combination with chemotherapy has resulted in an improvement in disease-free survival (DFS) and overall survival (OS), as well as a higher rate of pathological complete responses (pCR) [3–8], defined as the total absence of infiltrative component of the tumor in pathology analysis after post-neoadjuvant surgery (T0N0) [9]. pCR is also considered if there is only in situ component. The classification used to define pCR is that of Miller and Payne [10]:

Degree of local response:

- Grade 1 (pNR): no response.
- Grade 2 (pPR): minor reduction (less than 30%).
- Grade 3 (pPR): some reduction (between 30 and 90%).
- Grade 4 (almost pCR): marked reduction (greater than 90%).
- Grade 5 (pCR): absence of residual infiltrating cancer. There may be carcinoma in situ.

Degree of regional response:

- A: negative lymph nodes with no changes attributable to chemotherapy.
- B: positive lymph nodes with no post-chemotherapy changes.
- C: positive lymph nodes with evidence of partial response to chemotherapy.
- D: lymph nodes with post-chemotherapy changes and no residual involvement.

In recent years, most neoadjuvant clinical trials have used pCR as the primary endpoint of the study, demonstrating a statistically significant association between pCR and long-term prognosis: disease free survival (DFS) and overall sur-

vival (OS) [11]. Although the final diagnosis of pCR after neoadjuvant treatment is anatomopathological, control imaging tests prior to surgery provide information about the radiological response, with Nuclear Magnetic Resonance (MRI) being the preferred modality [11]. It is important to know if there is a correlation between the radiological response and pCR. The radiological classification used is the GEICAM group one [12]:

• NR (No Response): when no changes are observed or progression is observed.

• Minor PR (Minor Partial Response): reduction in tumor size less than 50%.

• Major PR (Major Partial Response): reduction in tumor size greater than 50%.

• CR (Complete Response): absence of residual tumor.

Several clinical trials such as NeoSphere, TRYPHAENA, KRISTINE or PAMELA have shown that neoadjuvant treatment has a similar efficacy to adjuvant treatment in terms of EFS and OS [8]. However, the administration of chemotherapy and anti-HER2 therapy prior to surgery has multiple benefits including facilitating surgical resection and the aesthetic result of surgery, increasing the rate of breast-conserving surgeries, evaluating tumor chemosensitivity *in vivo*, identifying predictive response biomarkers and carrying out early treatment on micrometastases. Studies indicate that pCR also has prognostic value, being an indicator of long-term survival [8, 13].

Of interest to us in the present study is evidence from phase II clinical trials which supports the neoadjuvant use of the combination of pertuzumab and trastuzumab added to chemotherapy to improve the rates of pCR [14]. NeoSphere, TRYPHAENA and other trials concluded that the administration of pertuzumab as part of the neoadjuvant treatment of localized or locally advanced HER2-positive breast cancer achieved a higher rate of pCR. There are no conclusive data on long-term DFS and OS results [7, 8, 10, 12].

The main objective of the present study was to analyse whether the trastuzumab-pertuzumab dual blockade, used as neoadjuvant therapy in patients with HER2-positive breast cancer (stages IIA–IIIC), shows an improved pCR (T0N0) relative to patients receiving a single blockade with trastuzumab. Taking into account the characteristics of the patient, neoadjuvant treatment patterns and types of surgery, additional objectives consisted in evaluating the correlation between pCR and radiological response for the two treatments, evaluating adverse effects and the safety profile and calculating added cost.

2. Material and methods

2.1 Study design and population

A prospective cohort study group consisted of patients at San Pedro's Hospital in Logroño (La Rioja, Spain) diagnosed with HER2 positive breast cancer. The patients were candidates for the dual trastuzumab/pertuzumab dual block neoadjuvant therapy treatment program initiated in May 2017, with patients recruited until May 2020. The patients received chemotherapy, mainly with anthracyclines and taxanes. The control group was derived retrospectively from patients with HER2 positive breast cancer who had neoadjuvant therapy with single block trastuzumab added to chemotherapy with anthracyclines or taxanes from the period prior to instituting the dual block treatments (prior to May 2017).

The inclusion criteria were: patients over 18 years of age with HER2 positive breast cancer, diagnosed at San Pedro's Hospital during the years 2008–2020, stages IIA–IIIC (FIGO), candidates for neoadjuvant therapy and with available data on the evaluation of the response. The main exclusion criteria were: pluripathological patients not candidates for complementary chemotherapy (denied by Oncology Service), patients older than 90 years, patients with a LVEF less than 52%, patients with bilateral breast cancer and relapses of breast cancer prior to the period studied.

The research was conducted in accordance with Good Clinical Practice standards and the current revision of the Declaration of Helsinki. There was no financial compensation for the participants or funding for the research team. The study was approved by the Research Ethics Committees of La Rioja, Spain (CEImLAR) with the study reference code EPA SP 108. Written informed consent was provided to all patients.

2.2 Sample size and sampling procedure

All patients that met the inclusion criteria were collected consecutively from May 2017 (start of the dual block program) and throughout the data collection period without sampling. Deceased patients were also eligible, to avoid selection bias in the study findings. An initial sample size of 60 patients was anticipated while 78 were eventually included in the study (39 dual block and 39 controls with single block). The control group was also selected without sampling, retrospectively in a retrograde manner from patients treated prior to the initiation of the double block program.

2.3 Statistical analysis

Data was collected in accordance to privacy policies. IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. (IBM Corp, Armonk, NY, USA) was used for further statistical analysis. In all statistical tests, $p < 0.05$ was considered as the reference value of significance.

For the descriptive analysis, the categorical variables were expressed with their frequencies and percentages. The correlation study was made of Pearson correlation.

The Logit model is a non-linear model which was used in the regression analysis. It indicates the probability that an event will occur (indicated by the dependent variable) when the explanatory variables increase by one unit. It is expressed by a logistic regression function to analyse the probability when we have dependent and categorical variables without normal distribution. As the dependent variable (pathological response) is categorical, we have to use the Logit model for the analysis of the relationship of dual block treatment with

a pCR. It takes a value of "1" if there is a pathological complete response, that is, absence of residual infiltrating cancer (Grade 5-pCR) and a value of "0" in the case of no response (Grade 1-pNR).

We used the study group and control group as the independent variables of interest indicating the specific treatment that each patient has received. It takes a value of "1" if they have received dual block (PT) and a value of "0" in the case of single block (T).

In addition, we also included other control variables such as age, hormonal treatment, type of surgery, development or not of menopause, and family history. Not all the variables collected were included to avoid problems of multicollinearity (variables that explain the same thing) or endogeneity (independent variables that explain each other). Our Logit model could be formulated mathematically in the following way:

$$Prob\ (ResponseAP = 1) = F\left(\beta_0 + \beta_1 \times T/PT + \beta_j Z_j\right) \quad (1)$$

In this mathematical formula, "T/PT" is the treatment variable (variable of interest) and "Zj" is the set of control variables. Furthermore, F = $\frac{exp\,(\beta)}{1+\exp\,(\beta)}$ where "β" is the set of estimated coefficients. This formula was used to estimate the probabilities.

If the estimated coefficients ("β") are positive, the probability that the answer is complete increases. Furthermore, to avoid biases, we carried out a robust estimation of heteroscedasticity, in such a way that the coefficients were not affected by heteroscedasticity or autocorrelation problems.

To calculate the additional costs to implementing the dual block neoadjuvant therapy was necessary to take a standard 65 kg patient for. Treatment with trastuzumab alone involved 18 cycles in total, the first being at a dose of 8 mg/kg and the remaining 17 at intervals of 21 days at a dose of 6 mg/kg.

Table 1. Patient demographic and medical data.

Characteristic	Single T block	Dual TP block
	n (%)	n (%)
Median age	51.71	52.76
Median tumor size	4.99	4.31
Family history of breast cancer	9 (23.07%)	17 (43.58%)
Caucasian	33 (84.61%)	33 (84.61%)
Smoking habits	4 (10.25%)	4 (10.25%)
Premenopausal	12 (30.77%)	9 (23.07%)
Median age of menarche	12.56	12.71
Hormonal treatment	14 (35.89%)	14 (35.89%)
Breastfeeding	24 (61.53%)	23 (58.97%)
Without concomitant diseases	21 (53.84%)	15 (28.46%)
Cardiovascular events	11 (28.20%)	14 (35.89%)

3. Results

3.1 Descriptive analysis

Table 1 shows the characteristics of the study group (dual TP block) and the control group (single T block). Regarding the stage, the most prevalent was IIB in control group and the mode in the study group was IIA stage.

Table 2. Study details and treatment responses.

	Single Block	Dual PT block
	n (%)	n (%)
Radiological response		
No response	4 (10.25%)	0
Minor partial response	9 (23.07%)	0
Major partial response	12 (30.76%)	19 (48.71%)
Full response	14 (35.89%)	20 (51.28%)
Total	39 (100%)	39 (100%)
Anatomopathological response		
Grade 1. No response	7 (17.94%)	1 (2.56%)
Grade 2. Reduction less than 30%	5 (12.82%)	0
Grade 3. Some reduction	8 (20.51%)	4 (10.25%)
Grade 4. Marked reduction	9 (23.07%)	7 (17.94%)
Grade 5. Pathological complete response	10 (25.64%)	27 (69.23%)
Total	39 (100%)	39 (100%)
Miller and Payne		
1B	7 (17.94%)	1 (2.56%)
2B	1 (2.56%)	0
2C	2 (5.12%)	0
2D	2 (5.12%)	0
3A	2 (5.12%)	0
3B	1 (2.56%)	1 (2.56%)
3C	3 (7.69%)	3 (7.69%)
3D	3 (7.69%)	0
4A	0	1 (2.56%)
4C	5 (12.82%)	1 (2.56%)
4D	3 (7.69%)	5 (12.82%)
5A	0	11 (28.20%)
5C	2 (5.12%)	2 (5.12%)
5D	8 (20.51%)	14 (35.89%)
Total	39 (100%)	39 (100%)
Surgery		
Tumorectomy + sentinel ganglion	1 (2.56%)	11 (28.20%)
Mastectomy + sentinel ganglion	4 (10.25%)	3 (7.69%)
Tumorectomy + axillary lymphadenectomy	15 (38.46%)	16 (41.02%)
Mastectomy + axillary lymphadenectomy	19 (48.71%)	9 (23.07%)
Total	39 (100%)	39 (100%)
Histological type		
Ductal infiltrating	37 (94.87%)	37 (94.87%)
Lobulillar infiltrating	2 (5.12%)	0
Inflammatory	0	1 (2.56%)
Mucinous infiltrating	0	1 (2.56%)
Total	39 (100%)	39 (100%)

The study details and treatment responses when comparing the dual TP block group and the single T block group are presented in Table 2. If we look at the radiological response, in single T block group 35.89% presented a full response and

51.28% in the case of dual PT block. A greater partial response (tumor reduction more than 50%) was produced 30.76% in the first group and in the last group it was a 48.71%.

On the other hand, in the case of the anatomopathological response, 25.64% of the patients of the single T block group presented a grade of 5, that is, absence of residual infiltrating cancer. While both the single block and the dual block provide a treatment for this type of tumor, the rate of pCR in the dual block group was 69.23% and in the single block group 25.64%. From this we can conclude that, in the dual treatment group, for more than half of the patients, the tumor disappeared completely.

Greater variability is observed in the Miller and Payne classification variable, although we observed that between 20–30% obtained a "5-D" score in both groups, which represents a complete local and regional response (tumor and lymph node).

The most performed surgery in the single T block group was mastectomy with axillary lymphadenectomy (48.71%) and, in the dual PT block group it was the tumorectomy with axillary lymphadenectomy (41.02%), leaving the performance of selective sentinel lymph node biopsies for axillary staging in the background. This shows the possibility to increasingly perform conservative breast surgery by doing dual block instead of single block, although the axillary lymphadenectomy still continues to be necessary. 94.87% of the sample presented infiltrating ductal histology and 60.96% were hormonal receptor positive (Luminal B-like molecular subtype) and 39.04% of the sample was hormonal receptor negative (pure overexpressed HER2 neu).

The most frequent adverse effects were asthenia, mucositis, nausea, vomiting and gastroesophageal reflux, with combinations of these in most patients.

Regarding survival, 80.77% of the sample met criteria for disease-free survival greater than 6 months after completing treatment, and 10.26% had died from breast cancer, none of them in dual PT block.

3.2 Correlations

In Table 3 we show the correlation matrix between all of the more relevant variables. It should be noted that the Pearson correlation coefficient between the radiological response and the pathological response for the combined patient groups is 0.67 representing the highest correlation coefficient observed among all the variables. The relationship between these responses is high, and since the coefficient is positive, both variables respond in the same direction. That is, a positive radiological response would be associated with a positive anatomopathological response, and vice versa.

The correlation coefficient between the radiological response and the pathological response increases to 0.87 when we consider only the dual-block treatment instead of the entire sample as a whole. With this we ratify the first of the specific objectives: there is a greater correlation between radiological and pathological response in dual block group.

It should also be noted the positive correlation coefficients of both responses with the treatment, which would indicate a certain relationship between the type of treatment and the response. We will check this next through a regression analysis.

3.3 Regression analysis

We can verify, as shown in Table 4, that the estimated coefficient is positive (2.272) and significant at 1% (p-value less than 0.01). This indicates that dual-block treatment increased the probability that the response would be complete, that is, that the cancer would disappear completely. In this way, we were able to achieve the main objective of this study: to determine whether the trastuzumab-pertuzumab dual blockade used as a neoadjuvant in patients with HER2-positive breast cancer (stages IIA–IIIC) achieved a greater pathological complete response (T0N0). In addition, we observed that the probability of a complete response with dual blockade is 0.98, while the probability with single blockade is 0.91, making a complete response more likely when dual blockade is administered.

To complete our study, we introduced the radiological response into the regression to verify that there is a positive relationship between the two, as indicated by the correlation coefficients.

As shown in Table 5, the estimated coefficient of radiological response is significant at 1% and positive. This confirms that a complete radiological response increased the probability that there was also a pathological complete response.

Regarding the control variables, it should be noted that having received some type of hormonal treatment, having a family history of breast cancer, breastfeeding and mastectomy-type surgery with axillary lymphadenectomy also increased the probability that the response to treatment would be complete and would demonstrate statistical significance (Table 6).

3.4 Safety profile

Table 7 details the frequency of adverse effects according to the type of treatment.

We can see that the side effects were fairly similar in the two treatment groups, although we note some difference. Mucositis and nausea, vomiting and gastroesophageal reflux were more frequent in patients with dual blockade, while cardiac events and febrile neutropenia were more frequent with single blockade. Patients tended to exhibit combinations of adverse effects and an analysis of this feature is presented in Fig. 1.

Notably, there are three adverse effects that have not appeared in any of the patients in the sample: reduced platelet count, anemia and hypokalemia.

With this we can affirm that the safety profile is quite similar in both groups, both types of treatment being generally well tolerated.

Table 3. Correlation matrix.

	T/PT Group	Age	Family history	Tobacco	Lactation	Hormonal treatment	Menopause	Tumor size	RX response	AP response	Surgery
T/PT group	1.0000										
Age	0.0689	1.0000									
Family history	0.2176	–0.0291	1.0000								
Tobacco	0.1383	–0.0752	0.1590	1.0000							
Lactation	–0.0342	–0.0076	–0.1530	–0.0051	1.0000						
Hormonal treatment	–0.0000	0.2878	–0.1512	–0.1987	0.1820	1.0000					
Menopause	–0.0177	0.1838	–0.0250	0.2006	–0.1074	–0.1607	1.0000				
Tumor size	–0.1588	–0.0285	0.0208	–0.0702	0.2530	0.0496	–0.1476	1.0000			
RX response	0.3502	–0.3504	0.0108	0.1238	–0.2007	–0.1237	0.1936	–0.0861	1.0000		
AP response	0.4690	–0.0499	0.1827	0.1897	–0.1573	–0.0246	–0.0279	–0.2346	0.6702	1.0000	
Surgery	–0.3607	0.0840	–0.0528	0.0039	–0.0387	0.1795	–0.0864	0.4404	–0.2562	–0.2817	1.0000

Table 4. Logit regression results for dual block PT and single block T (* $p < 0.01$).**

pCR	Odds ratio	*p*-value
T/PT	2.272***	0.002
	(0.744)	
Constant	−2.153	
	(1.419)	
Control variables	YES	
Patients (n)	78	

Table 5. Relationship between radiological and pathological response (* $p < 0.01$).**

pCR	Odds ratio	*p*-value
T/PT	2.369***	0.004
	(0.831)	
RX response	2.854***	0.002
	(0.942)	
Control variables	YES	
Patients	78	

Table 6. Control variables and response to treatment.

Variables	pCR
Trastuzumab/pertuzumab-trastuzumab	2.272***
	(0.744)
Family history of breast cancer	1.522**
	(0.772)
Concomitant diseases	−0.117
	(0.786)
Breast feeding	1.385*
	(0.842)
Hormone treatment	1.700*
	(0.936)
Menopause	0.537
	(1.050)
Tumor size	−0.196
	(0.181)
Molecular type	−2.616***
	(0.883)
Mastectomy + axillary lymphadenectomy	3.214**
	(1.399)
Constant	−2.153
	(1.419)
Patients (n)	78

Robust standard errors (***$p < 0.01$, **$p < 0.05$, *$p < 0.1$).

3.5 Treatment costs

Calculating that 150 mg of trastuzumab costs €507.30, the total cost of treatment with 18 cycles for a patient was €24,181.30. By comparison, treatment with trastuzumab-pertuzumab also involved a total of 18 cycles. In the first 4 cycles performed in neoadjuvant treatment both compounds were given, costing €4579 for the first cycle of pertuzumab (840 mg) and €2289.5 for the remaining three cycles (420 mg). Following this, 14 more cycles with only trastuzumab at a dose of 6 mg/kg were administered. The total cost of the treatment of 18 cycles of dual blockade (4 cycles of trastuzumab-pertuzumab and 14 subsequent cycles of trastuzumab) amounted to €35,189.14.

Table 7. Percentage of adverse effects according to treatment.

	Single block (%)	Dual block (%)
Febrile neutropenia	33.34%	25.64%
Neutropenia	23.08%	15.38%
Asthenia	46.16%	41.20%
Diarrhea	33.32%	33.34%
Cardiac event	7.70%	0.00%
Mucositis	41.02%	58.98%
Nausea, vomiting	30.78%	38.46%
Neurotoxicity	15.38%	12.82%

4. Discussion

The pathological complete response in the dual block group was higher than in the single block group (69.23% versus 25.64%), indicating the addition of pertuzumab to be more effective in the neoadjuvant treatment of HER2 positive breast cancer.

The main objective of this work was to analyse whether the trastuzumab-pertuzumab dual block used as neoadjuvant treatment in patients with HER2-positive breast cancer (stages IIA–IIIC) achieved a better pathological complete response (T0N0) than in those patients receiving single block treatment with trastuzumab. A literature review of related studies using HER2 dual block indicated higher pCR rates: 58.5% compared to 49.2% achieved with other treatments (single block, taxanes and dual block or only taxanes) [4, 8].

Our study suggests that the regimen that includes dual blockade in neoadjuvant treatment with trastuzumab and pertuzumab added to chemotherapy with anthracyclines and taxols, is the most effective treatment for HER2 positive breast cancer, producing a better pathological complete response than achieved in the main TRYPHAENA study, KRISTINE, NeoSphere, PAMELA, Opti-Her HEART, BERENICE and NEOPETRA [4–6, 8, 15–17]. The pCR rate obtained in our study in patients with single block was 26.01%, but that obtained in the dual block cohort was 69.23%, higher than that reported in the aforementioned clinical trials where the pCR rate is between 40–60%.

Most studies have identified a correlation between radiological and pCR similar in either dual blockade or single block cases [11–14]. We evaluated this in our study as one of the stated objectives. We found the correlation coefficient, taking into account the entire sample of 78 patients, was positive at a value of 0.67. However, based only on the patients treated with dual blockade the correlation coefficient reached

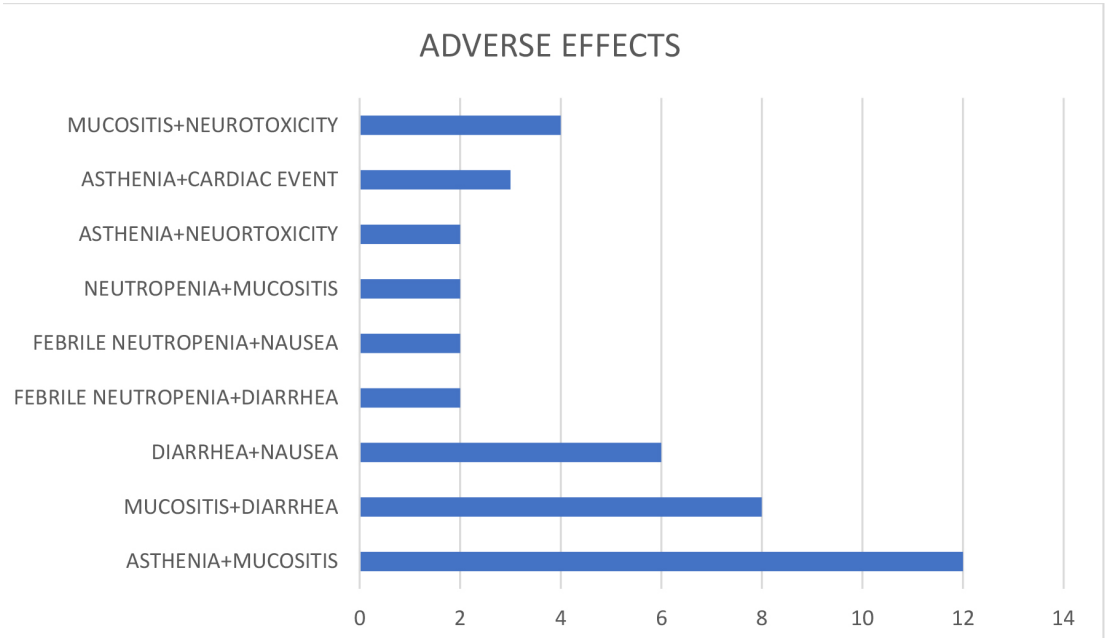

Fig. 1. Combinations of adverse effects.

0.87. Thus, there was a higher correlation between radiological and pathological response in the dual blockade group.

Regarding the safety profile, among the 78 recruited patients, only 3 cases of cardiac events were observed, none of them belonging to the dual block group. The left ventricular ejection fraction (LVEF) was not altered in any patient, remaining above 52% in both treatment groups. This observation is contrary to a number of other studies of dual block including TRYPHAENA, BERENICE and OPTI-HER HEART. where the cardiac event rate although low was still present [4, 15, 16].

The frequency of other adverse effects agrees with those reported in these trials [15, 16, 18], the most frequent being asthenia, mucositis, nausea and vomiting. These results suggest that the safety profile of dual blockade is very similar to that of single block. Thus, we achieved improved efficacy without adding significant adverse effects.

The last specific objective was intended to estimate treatment cost increase for the dual block procedure. Treatment with trastuzumab-pertuzumab adds approximately €11,788.84 per person making the dual block treatment 45.52% more expensive than the single block. We believe that the increased cost of treatment with the use of dual blockade is justified since the pathological complete response rate is 2.7 times higher than in single block and this implies increased survival without causing serious side effects. However, due to its high price, dual block might be appropriate in cases where maximum benefit will be obtained.

The small population base in La Rioja and the requirement of the patients to meet a number of inclusion and exclusion criteria, including HER2 positivity, led to a relatively small study population for the study and is one of the limitations of this investigation. Nonetheless a strength of this study is that our pCR rate of 69.23% is higher than that observed in the main trials in the literature [4–6, 8, 15–17] and the results achieved statistical significance. We plan to continue our surveillance of the patients in this study with a goal of obtaining medium- and long-term survival statistics and further evaluating the cost effectiveness of the treatments.

5. Conclusions

The pathological complete response was greater in the dual block group than in the single block group (69.23% versus 25.64%), indicating this treatment to be more effective in the neoadjuvant treatment of HER2 positive breast cancer. Besides this, the correlation between radiological and pathological response was higher in patients with dual blockade, reaching a Pearson correlation coefficient of 0.87. Safety profile was similar in both groups, with no incidence of serious cardiac events and the additional cost with the use of dual blockade seems justified by the significantly higher pCR.

It would be necessary to expand the sample size and increase the study time to perform an adequate cost-effectiveness and survival analysis.

Author contributions

ACRP, BDE, SMA and MJPM designed the research study. ACRP performed the research. MJPM provided help and advice on the experiments. ACRP, MLO and CFG analyzed the data. ACRP, BDE and SMA wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This research work has been carried out in accordance with the rules of good clinical practice with full acceptance of current ethical standards (Declaration of Helsinki). This work has the classification resolution of the Spanish Agency for Medicines and Health Products (AEMPS) as "Prospective Follow-up Post-Authorization Study" (EPA-SP) with code MPM-PER-2019-01, as well as the approval of the La Rioja Drug Research Ethics Committee (CEImLAR) with CEImLAR EPA SP 108 reference. All subjects gave their informed consent for inclusion before they participated in the study.

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Conflict of interest

The authors declare no conflict of interest.

Availability of data and material

All data will be obtained retrospectively from the medical electronic records of the patients thanks to the help of the Pharmacy Service, who provided a list with all the patients treated with pertuzumab (hospital dispensing medication).

Code availability

All data from the Electronic Health Record of the Selene hospital computer program will be collected. All data will be compiled in a data collection sheet.

These data will be analysed through a database using Microsoft Excel 2011 software and with the SPSS statistical program.

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