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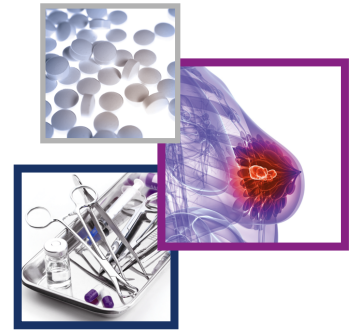

Real-world data of subcutaneous trastuzumab and intravenous pertuzumab as neoadjuvant therapy for localized HER2+ breast cancer in Panama

Franklin Castillero Rodriguez*[,1], Omar Castillo-Fernandez[1,2], Maria Lim-Law[1], Cristiane Martin Palacios[1], Lilian Montano[1], Stephanie Benitez[1] & Jaime Samudio[1]

[1]Department of Medical Oncology, Instituto Oncologico Nacional de Panama, Panama City, Panama

[2]Medicine Department, Medicine School, University of Panama, 0824-10

*Author for correspondence: mdcastillerofranklin@gmail.com

The aim of this study is to determine the effectiveness of subcutaneous trastuzumab in combination with intravenous pertuzumab and chemotherapy for patients with HER2-overexpressing localized breast cancer treated in our center. **Methods:** This was a descriptive, retrospective, real-world study. **Results:** Of 156 patients, pathological complete response (pCR) was achieved in 64.1%. A multivariate analysis showed a relationship with a negative hormone receptor (HR) expression and a HER2 score of 3+ by immunohistochemistry. Relapse-free survival (RFS) was higher in patients with pCR. **Conclusion:** Neoadjuvant therapy with dual blockade using intravenous pertuzumab and subcutaneous trastuzumab for HER2+ localized breast cancer in routine clinical practice resulted in a 64.1% pCR rate. Additionally, this outcome was related to a negative HR expression and HER2 overexpression, and correlated with higher relapse-free survival.

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Keywords: anthracyclines • breast cancer • disease-free survival • effectiveness • neoadjuvant therapy • pathological complete response • pertuzumab • real-world data • toxicity • trastuzumab

Breast cancer is the commonest type of cancer in women, with nearly 2.1 million cases reported worldwide in 2018 [1]. According to the National Cancer Registry of Panama, breast cancer is also the most common cause of cancer in Panamanian women, with an incidence of 62.3/100,000 and an annual mortality rate of 11.3/100,000 inhabitants [2]. Additionally, a previous analysis showed a higher incidence and mortality trend in the last decade, with an annual percentage change of 2.66% [3]. Hence breast cancer is considered a public health issue in this country. Most of these patients are treated at the Instituto Oncologico Nacional. Neoadjuvant chemotherapy is a widely used approach for large/aggressive tumors, allowing downstaging and breast-conserving surgery [4].

HER2 is overexpressed in about 25–30% of all breast cancers [5] and is associated with a clinically aggressive disease with a poorer prognosis [6]. Trastuzumab and pertuzumab are monoclonal antibodies directed to the extracellular part of the HER2 receptor. The former is directed at domain IV of the extracellular portion, inhibiting HER2-mediated proliferation, signaling and angiogenesis; and the latter at domain II, blocking HER2 receptor dimerization with other HER family members, thus inhibiting the downstream signaling process related to cell proliferation [7].

Neoadjuvant chemotherapy is a widely used strategy for localized breast cancer, downstaging the tumor, allowing breast-conserving surgery and eradicating micrometastatic disease. One meta-analysis showed no differences in relapse-free survival (RFS) and overall survival between the neoadjuvant and adjuvant approaches [8]; however, neoadjuvant therapy may lead to a pathological complete response (pCR), which has been accepted as a surrogate marker for longer survival [9].

In HER2-overexpressing localized breast cancer, neoadjuvant treatment with trastuzumab has demonstrated a higher pCR and an improved survival compared with patients receiving chemotherapy alone [10]. Therefore

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a meta-analysis suggested that a higher rate of pCR is reached in patients with HER2-overexpressing breast cancer treated with trastuzumab-containing neoadjuvant chemotherapy, and that this strongly correlates with an improved event-free survival [11].

Trastuzumab and pertuzumab (dual HER2 blockade) in combination with chemotherapy has also been studied in the neoadjuvant setting, and many trials have demonstrated a higher pCR with this strategy compared with trastuzumab alone [9,12]. This outcome had also been correlated with a negative hormone receptor (HR) expression [11].

After the HANNA trial, the subcutaneous (sc.) presentation of trastuzumab was approved in our institution; given its higher cost–effectiveness [13] and higher patient preference [14], we started using it for our patients with localized HER2-overexpressing breast cancer at a fixed dose (600 mg sc.), in view of the safety profile previously reported [15]. Because of the lack of availability of sc. pertuzumab in our country, we decided to give it by intravenous (iv.) administration. The aim of this study was to determine the effectiveness of sc. trastuzumab and iv. pertuzumab as neoadjuvant dual blockade for locally advanced HER2-overexpressing breast cancer in our institution between 2015 and 2019.

Patients & methods

Design & main objective

This is a retrospective, single-center, descriptive study. The main objective was to determine the pCR rate and determine whether it was widely divergent from the rates documented in prior studies; this was defined as the absence of viable tumor in breast or lymph nodes, while the presence of *in situ* carcinoma was permitted (ypT0/isypN0). The secondary outcomes were RFS (defined as time between surgery and documented clinical relapse) and the reported toxicity.

Data source

We used the electronic medical records of our institution to identify patients with newly diagnosed HER2-overexpressing localized breast cancer between January 2015 and June 2019. The electronic chart provided deidentified information about patient history, demographics, pathology-specific details and treatment received, and information about relapse or progression of the disease and overall survival. This study was approved by our institutional ethical board.

Patient selection & statistical analysis

We included patients aged ≥18 years with histologically confirmed breast cancer and HER2 overexpression detected by immunohistochemistry (IHC) or FISH in the Instituto Oncologico Nacional, from January 2015 to June 2019, who received neoadjuvant therapy with sc. trastuzumab, iv. pertuzumab and chemotherapy. We excluded patients in whom breast surgery was not performed, or who were lost to follow-up or completed the treatment outside the institution. The operational definition of HR positivity was at least 1% positivity of the examined nuclei in the tumor sample. Patient staging was performed clinically; every patient had been assessed in a multidisciplinary team including an oncology surgeon, medical oncologist and radiologist. Ultrasonography of the axilla was not mandatory for staging, and tomography was usually used to rule out distant metastases.

The Kaplan–Meier method was used to estimate unadjusted survival times, which were compared between clinicopathological variables using the log-rank test. Cox proportional hazard regression analysis was performed to estimate the hazard ratio by the presence of pCR. The relation between pCR and categorical variables was studied by the chi–square test, with the Student t test for the continuous variables. A binary logistic regression was used for univariate analysis between pCR and clinicopathological variables. We selected those with a statistical significance or a trend for an association. Then we elaborated a model for a multivariate analysis adjusting for HR status, HER2 overexpression (detected by FISH or with a score of 3+ by IHC) and tumor size <10 cm. A p-value of <0.05 was considered statistically significant. The analysis was performed using SPSS v. 24 (IBM Corp., NY, USA).

Results

A total of 156 patients met the inclusion criteria in this study. Median age was 52 years (range: 40.2–63.8), the median tumor size was 6.0 cm, 39.7% were high-grade tumors and 52.3% of the patients had HR+ expression. Other baseline characteristics are described in Table 1. A total of 27 patients (17.3%) were managed with a surgically conservative approach.

Table 1. Baseline characteristics (n = 156).

Characteristic	Value
Age (years; median/range)	52 (40.2–63.8)
Tumor size (cm; median/range)	6.0 (1.5–22.0)
Histological grade	n (%)
– Grade 1	3 (1.9)
– Grade 2	88 (56.4)
– Grade 3	62 (39.7)
Hormone receptor expression	
– Positive	83 (53.2)
– Negative	73 (46.8)
Tumor clinical stage	
– T1	13 (8.3)
– T2	33 (21.2)
– T3	77 (49.4)
– T4	30 (19.2)
Lymph node clinical stage	
– N0	34 (21.8)
– N1	92 (59)
– N2	22 (14.1)
– N3	8 (5.1)
Clinical stage	
– I	3 (1.9)
– II	52 (33.3)
– III	97 (81)
– IV	3 (1.9)
Neoadjuvant regimen	
– Anthracycline-based	150 (96.1)
– Non-anthracycline-based	6 (3.8)

A pCR of 64.1% was reached in our population, with a difference according to HR expression (73.9% in HR- patients vs 55.4% for HR^+ patients; p = 0.019) and HER2 overexpression (66.7% in HER2 3+ by IHC vs 22.2% in HER2 2+ and confirmed by FISH; p = 0.011; Figure 2). In the univariate analysis, patients without HR expression had an odds ratio of 2.28 (95% CI: 1.16–4.51) for pCR, and there was also an association with HER2 3+ and pCR, with an odds ratio of 7.0 (95% CI: 1.40–34.9). The pCR rate was not related to tumor size, but there was a trend for a lower rate in tumors ≥10 cm (odds ratio: 0.46; 95% CI: 0.18–1.17; p = 0.07; Table 2). In the multivariate analysis, only negative HR expression and HER2 overexpression were correlated with a higher pCR (Table 2).

With a median follow-up of 29.4 months after surgery, there were 27 relapses, 19 of them in patients without pCR. The median RFS was related to the presence of pCR, with a hazard ratio of 0.22 (95% CI: 0.09–0.51; p < 0.001; Figure 1).

Regarding toxicity, 26 patients (16.7%) had a decline in left ventricular ejection fraction, of whom three suspended therapy because of clinical heart failure. Additionally, grade 1–2 diarrhea was reported in 16 patients (10.2%).

Discussion

This real-world evidence suggests that neoadjuvant systemic therapy based on sc. trastuzumab and iv. pertuzumab confers similar outcomes to the iv. formulations, with good tolerability. Regarding dual blockade and pCR, the NEOSPHERE trial suggested an association between this outcome and longer progression-free survival, but only 23% of the entire population reached it [9]; however, in a subgroup analysis, a numerically higher pCR was reached in the HR- population. Later, the TRYPHAENA trial demonstrated a pCR rate of 50% in patients receiving 5-Fluoroacil, epirubicin, cyclophosphamide + docetaxel + trastuzumab + pertuzumab (FEC–THP), and a disease-free survival ratio of 0.27 (0.11–0.64) for pCR, which was defined by the absence of invasive neoplastic

Table 2. Analysis of clinicopathological factors and pathological complete response.

Univariate analysis			
Variable	**OR**	**95% CI**	**p-value**
Negative HR expression	2.29	1.16–4.51	0.02
HER2 overexpression (3+ by IHC vs FISH-detected)	7.0	1.4–34.9	0.02
Tumor size (≥10 cm)	0.46	0.18–1.17	0.07
Anthracycline exposure	1.12	0.20–6.34	0.89
Age <40 years	0.88	0.31–2.49	0.81
Grade 3 histology	1.22	0.62–2.39	0.56
Multivariate analysis			
Variable	**OR**	**95% CI**	**p-value**
Negative HR expression	2.22	1.09–4.49	0.048
HER2 overexpression (3+ by IHC vs FISH-detected)	6.02	1.18–3.06	0.029
Tumor size ≥10 cm	0.41	0.16–1.08	0.051

HR: Hormone receptor; IHC: Immunohistochemistry; OR: Odds ratio.

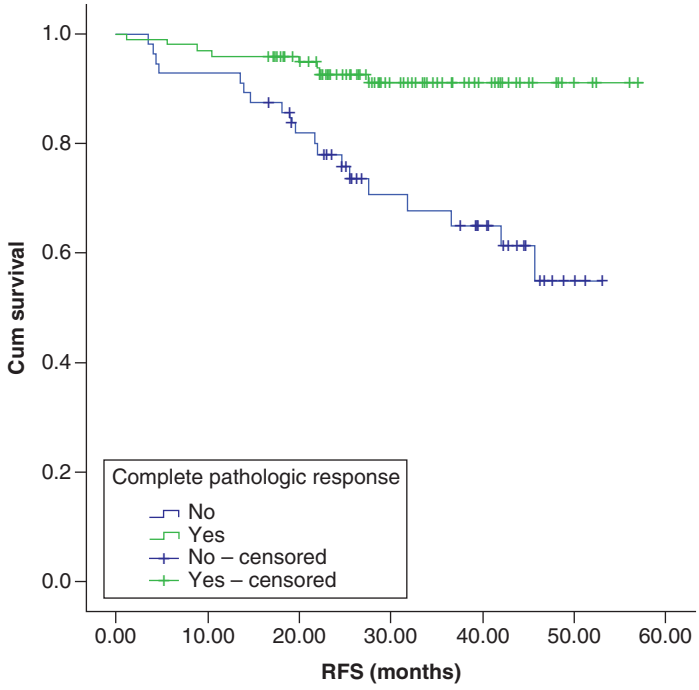

Figure 1. Relapse-free survival by pathological complete response status. Median still not reached. Hazard ratio for relapse = 0.22 (95% CI: 0.09–0.51; p = 0.001). HR: Hormone receptor; RFS: Relapse-free survival.

cells during evaluation of the primary tumor or in the axilla (ypT0, ypN0) [12]. However, an exploratory analysis of this trial failed to find any predictive marker of pCR using HER2-directed dual blockade [16]. Additionally, the NEOALTTO trial found that patients without HR expression were more likely to reach a pCR (p = 0.0005) but in patients receiving a combination therapy of trastuzumab, lapatinib and chemotherapy [17]. Given these results, additional information regarding predictors of pCR when using HER2 dual blockade and chemotherapy is needed.

Little retrospective, descriptive, real-world evidence has been published regarding HER2 blockade for breast cancer. Spring *et al.* reviewed 121 patients treated with the neoadjuvant approach in a large academic medical institution, where higher pCR was reached with the dense-dose adriamycin + Cyclophosphamide + taxanes + trastuzumab + pertuzumab (ddAC–THP) regimen (60%) versus dense-dose adriamycin + cyclophosphamide + taxanes + trastuzumab (ddAC–TH) (46%), with an association of HER2 3+ overexpression by IHC with pCR in a multivariate analysis using a logistic regression model [18]. However, the authors compared four different neoadjuvant regimens in their population and both trastuzumab and pertuzumab were given as an iv. formulation. In our trial, most of the patients received anthracyclines, and this could explain the higher pCR reached, given

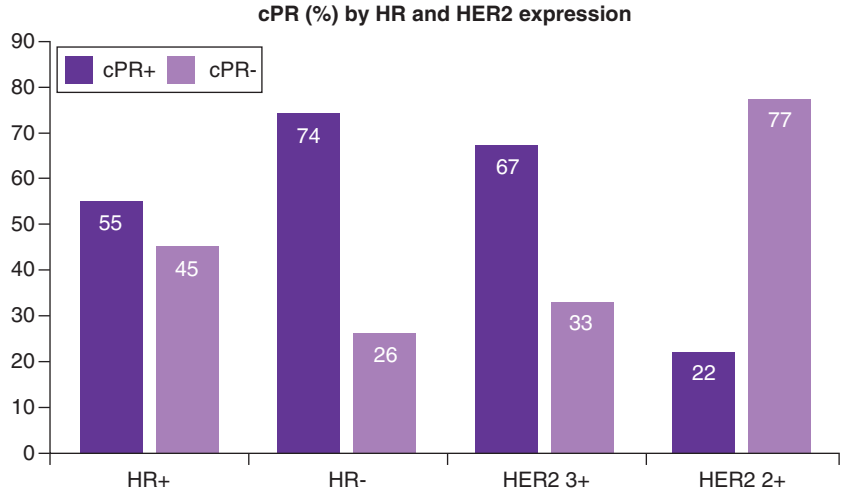

Figure 2. Pathological complete response by HR and HER2 expression by immunohistochemistry.
55% of patients with HR^+ disease reached pCR, while 74% of HR- disease reached pCR. Only 22% of patients with HER2 overexpression detected by FISH reached pCR.
HR: Hormone receptor; pCR: Pathological complete response.

the topoisomerase-II overexpression described in HER2-overexpressing breast cancer [19]. In another retrospective review by Singh *et al.*, 66 patients received AC followed by weekly paclitaxel/trastuzumab/pertuzumab, both in iv. formulations, and reached a pCR of 72% [20]. This supports our hypothesis, but that study found no association with HR expression, as we did here. Regarding the possible inverse association between tumor size and pCR, a previous report of 88 patients treated with paclitaxel/carboplatin/trastuzumab found no correlation [21]; however, most of the patients had tumors <5 cm (T2) and the median size was not reported. Most of our patients had T3/4 tumors, with a median size of 6.0 cm, but despite this, there was a benefit of dual blockade irrespective of tumor size among tumors <10 cm. As the tumor size increases, lower pCR rates are expected, and these data could suggest a cutoff of 10 cm for an incomplete treatment response. On the other hand, three patients included in our study had stage I disease. In those cases, the authors considered the potential benefit of a neoadjuvant approach, given the clinical information of this approach in patients with T2N0M0 disease [9], as has also been reported in other real-world data studies [18]; only two of them had a pCR.

Regarding the effect of pCR on RFS, a previous meta-analysis of 12 international trials demonstrated a lower RFS among patients with HR-, HER2-overexpressing breast cancer (hazard ratio: 0.15; 95% CI: 0.09–0.27) in those patients who reached pCR [11]. Our study, with admittedly a shorter follow-up, found a hazard ratio of 0.22, confirming the role of achieving this outcome in the prediction of a better survival.

Recently, the final analysis of the MetaPHER trial reported no new side effects, a consistent safety profile and an objective response rate of 75.6% with a regimen using sc. trastuzumab + iv. pertuzumab + docetaxel, supporting the use of this combination treatment in the metastatic setting [22]. But as far as we know there is no randomized trial regarding this combination in the neoadjuvant setting. Besides this, our center has implemented it as a standard strategy based in a previous reported cost-saving analysis, with a cost reduction of 17% and annual savings around $1.8 million [23].

Our study has many limitations that are intrinsically related to the retrospective methodology, such as the selection bias and the lack of randomization; additionally, we need a longer follow-up to get data regarding overall survival. Also, the information about side effects is limited because the measure of left ventricular ejection fraction was not mandatory and depended on the medical criteria. However, the statistical analysis of our patients supports the hypothesis of the positive association between negative HR expression and pCR, and the relationship between pCR and a longer RFS, with a safety profile with sc. trastuzumab in combination with iv. pertuzumab, supporting their use in the daily clinical practice, given its higher cost–effectiveness, in developing countries.

Conclusion

In conclusion, neo-adjuvant therapy for HER 2-overexpressed breast cancer with a regimen containing chemotherapy and sc. trastuzumab/iv. pertuzumab, is effective in the routinely clinical practice, allowing for a 64.1% of pCR and good tolerability, and could be considered an alternative if there is a lack of access for other presentations of these drugs.

Summary points

- Dual blockade with subcutaneous trastuzumab and intravenous pertuzumab in combination with chemotherapy in the neoadjuvant setting allows for a pathological complete response (pCR) rate of 64.1%.
- The pCR rate was higher in patients without hormone receptor expression and patients with HER2 expression of 3+ by immunohistochemistry.
- The pCR rate was also a surrogate for longer disease-free survival in our patients.
- The relatively high pCR rate in our study could be explained by anthracycline exposure in our patients.
- There was no correlation between initial tumor size and pCR, but there was a trend for a lower pCR rate in tumors ≥10 cm.
- Combining subcutaneous trastuzumab with intravenous pertuzumab is feasible, with good patient tolerability and few side effects.
- A low frequency of clinical heart failure was reported in our patients.
- Systemic regimens containing subcutaneous trastuzumab allow for a cost reduction, which could result in higher accessibility in developing countries for these drugs.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations

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