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Original Research Paper

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NEOADJUVANT THERAPIES FOR BREAST CANCER HER-2 POSITIVE: EXPERIENCE IN THE HOSPITAL ONCOLOGICO GRAL. SOLON ESPINOSA AYALA

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ABSTRACT

Objectives: to describe the demographic variables for breast cancer HER-2 positive in neoadjuvant treatment and evaluate the response to trastuzumab compared to chemotherapy alone.

Methods: a descriptive analysis of older women than 18 years old during the years 2010 and 2015 in which neoadjuvant chemotherapy was performed, evaluating the overall survival, the time of progression, the pathological response. The crossing of variables was performed using Chi-square, the survival estimate was made using the Kaplan Meier method and the survival functions were compared using the Log-Rank test.

Results: The neoadjuvant treatment was performed in 35 patients with stages II (11/31.4%) and III (24/68.6%), a pathologic complete remission (pCR) was achieved in patients treated with trastuzumab in (13 / 44.8 %), without reaching a statistically significant level. With respect to the rCP in regard to the immunophenotype HER2 + versus HER2 + / HR=hormonal receptor (36.4 vs 37.5 months), with respect to survival, no statistically significant differences were obtained, however, general survival was obtained an average of 81.4 months

Conclusion: although the main weakness of this study is that is a retrospective trial, in our institution with the TCH scheme we reached an acceptable rCP, so we are within the international standards in relation to the neoadjuvant, however, we must look for new Strategies such as sequential chemotherapy, double blockade of HER-2 and, in this way, improve the results.

KEYWORDS : Breast, cancer, Her2, neoadjuvant, Quito, Ecuador

INTRODUCTION

The breast cancer in Ecuador according to the national registry of tumors occupies the first place of incidence and the third in mortality. (1) more recent analyzes of study to 3 decades report that the breast cancer is increased among the women of Quito (2)

The human epidermal growth receptor factor (HER-2) oncogene was discovered in 1984, which encodes the transmembrane tyrosine kinase receptor, this type of receptor participates in the communication between cell and cell, and between cell and stroma in the process of signal transduction, this receptor dimerizes with several members of the family (HER-2, HER-3, HER-4) activating phosphorylation and signaling cascade. (3-8)

Women with breast cancer HER-2 have a higher risk of progression and death, which is why strategies have been developed to block this signaling pathway allowing control of this biologically more aggressive variety, in Ecuador it has been possible to determine in previous studies an overexpression or amplification of HER-2 in a range of 11.58% -14.3%, with a greater presence in women under 60 years old and little overexpression in indigenous or Afro-descendant women. (9.10)

Neoadjuvant therapy can reduce locally advanced breast cancer and improve breast conservation rates. In addition, it provides the opportunity to observe the capacity for in vivo response of cancer before surgical resection and to change therapy if an adequate response is not detected.

There are no previous studies in our country that demonstrate that the treatment of women with HER-2 positive breast cancer treated with Trastuzumab, improve overall survival, progression-free survival.

The objectives of this research are to describe the demographic variables, and to assess the response to trastuzumab in neoadjuvant treatment.

METHODOLOGY

Clinical records of the "Hospital Gral. Solón Espinosa Ayala" of 1010 women were reviewed during the years 2010 and 2015 with the diagnosis of breast cancer, of those women were selected only the neoadjuvant treatment.

The cases were identified through the National Registry of Tumors, of those women older than 18 years old, and confirmed diagnosis of early or locally advanced breast cancer with HER-2 overexpression

determined by immunohistochemistry or dual amplification by SISH when was necessary; considering stages IIB to IIIC as a locally advanced tumor.

A general descriptive analysis of the group of selected patients, overall survival, time of progression, pathological response to neoayuvance was performed, the results were obtained and described by means of absolute frequency determination and measures of central tendency. The crossing of variables was performed with contingency tables submitted to association using Chi-square statistics, the survival estimate was performed using the Kaplan Meier method and the survival functions were compared using the Log-Rank test.

The information obtained from the digital medical records was analyzed using the statistical package Excel and SPSS.

RESULTS

Neoadjuvant was performed in 35 patients; stages II (11/31.4%) and III (24/68.6%), of which 17 patients under 50 years of age and 18 patients older than 50 years; 29 patients were treated with chemotherapy plus trastuzumab (TCH) while 6 patients were treated with chemotherapy (TAC), it is important to indicate that only 11 patients had pure HER-2 status; data described in Table 1.

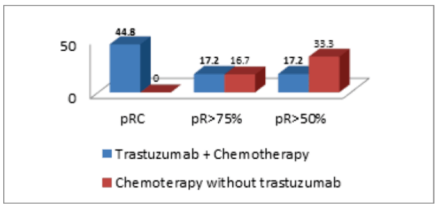
TABLE 1. Descriptive analysis of breast cancer HER-2

Variable		N	%
Age	< 50 Years	17	48.6
	> 50 Years	18	51.4
		35	100
LATERALITY	Right	19	54.3
	Left	16	45.7
		35	100
Clinical Stage	IIA	3	8.6
	IIB	8	22.9
	IIIA	12	34.3
	IIIB	11	31.4
	IIIC	1	2.9
	Total	35	100
Status	Dead	6	17.1
	Live	39	82.9
	Total	35	100
Pathology	DUCTAL	32	91.4
	LOBULAR	2	5.7
	PAPILAR	1	2.9
	Total	35	100
Histological Grade	1	5	14.3
	2	26	74.3
	3	4	11.4
		35	100
Race	LATINOAMERICAN	26	74.3
	INDIGENOUS	7	20
	AFRO ECUADOR	2	5.7
	Total	35	100
Treatment	TCH*	29	82.9
	TAC**	6	17.1
	Total	35	100
Neoadjuvant	HER2+	11	31.4
	RE***/HER2+	24	68.6
		35	100

* (Docetaxel / Carboplatin / Trastuzumab);
** (Docetaxel / Doxorubicin / Cyclophosphamid)
*** RE estrogen receptor

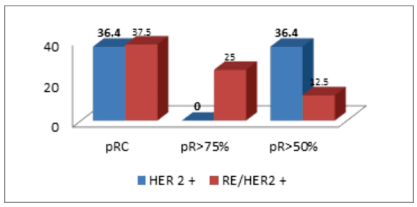
Of these 35 patients pathologic complete remission (pCR) was achieved in patients treated with trastuzumab in (13 / 44.8%) while no patient who received chemotherapy reached pCR, data represented in figure 1; while with regard to the luminal immunophenotype and pure HER-2 there is no statistically significant difference to reach a rPC, even more, presenting uneven groups in the contingency table as shown in figure 2.

Figure 1.-Pathological response (rP) to neoadjuvant treatment.



Chi square = 19.07; p = 0.001

Figure 2.- Pathological response in relation to pure HER-2 type or HER2 / RE



Chi-square = 7.23; p = 0.12

With regard to survival, no statistically significant differences were obtained, it was observed an average survival of 81.4 months, with some interesting data among them the lack of a statistically significant difference in terms of age (older or less than 50 years old), we also do not have greater difference in clinical stage, although higher survival is reported in those who do not reach clinical response is not statistically significant because only 3 patients are in this group and only 1 survives and causes statistical failure, something similar occurs in the group with pathologic remission (greater and less than 50%), whereas according to the immunophenotype more patients survive than over expressing HER-2 with a component luminal (HER-2/HR) than those that present pure HER-2; chemotherapy with trastuzumab improves survival than chemotherapy without monoclonal antibody, data that are best represented in table 2.

Variable	description		Survival	HR; IC 95%	p
Age	< 50 years old		78.2	6.9 (64.6-91.8)	0.2
	> 50 years old		81.9	4.4 (73.1-90.6)	
	Overall		81.4	4.6 (72.3-90.0)	
TNM	EII		57.2	6.1 (45.2-69.3)	0.7
	EIII		57.3	3.9 (49.5-65.1)	
	Overall		57.3	3.3 (50.8-60.3)	
rPC	pRC	N=13	56.7	5.6 (45.8-67.7)	0.2
	pR>75%	N=6	44.3	4.8 (34.7-53.9)	
	pR>50%	N=7	61.4	7.6 (46.4-76.3)	
	pR<50%	N=6	65.1	9.0 (47.4-82.9)	
	0%	N=3	67.0	.00 (67.0-67.0)	
	Overall	N=35	57.3	3.3 (50.8-63.8)	
IHQ*	HER 2 +		70.3	9.7 (51.2-89.4)	0.07
	RE/HER2 +		88.1	3.2 (81.7-94.5)	
	Overall		81.4	4.6 (72.3-90.5)	
TTO**	TCH		82.4	4.8 (73.0-91.8)	0.2
	TAC		71.2	12 (45.9-96.0)	
	Overall		81.4	4.6 (72.3-90.5)	

* Immunohistochemistry
**treatment

DISCUSSION

Since FDA approved trastuzumab in the adjuvant treatment in 2006, several trials have studied the benefit of adding trastuzumab to chemotherapy in the neoadjuvant treatment.

Since the advent of Trastuzumab, locally advanced breast cancer HER-2 has ceased to be an insurmountable threat, so much so that the NOHA trial showed for the first time that rCP rates almost doubled by adding a therapy directed against HER-2, (45 patients vs.

23 patients), whereas in this study rCP was obtained in 13 vs 0 patients, demonstrating an important benefit by adding Trastuzumab to chemotherapy as neoadjuvant treatment. (11)

Although for Buzdar et al, who has a similar sample of 34 patients receiving neoadjuvant disease, he describes the fact of a complete clinical response of 65% for patients treated with Trastuzumab plus chemotherapy versus 26% of patients treated with chemotherapy alone, whereas in the study GeparQuattro (Neoadjuvant Treatment with Trastuzumab in Breast Cancer HER2 Positive) was a large randomized, multicenter, phase 3 trial that evaluated neoadjuvant capecitabine in breast cancer, reported total pCR (ypT0 /pN0) in 41.4% of patients in the HER-2 + group, in our research we report a complete pathological response of 44.8% with chemotherapy plus trastuzumab vs 0% for those who only receive chemotherapy, so we can say that in our institution with the TCH scheme we are within the international standards in relation to neoadjuvant. (5,12,13)

When reviewing the pCR rates reported for different trials, it is important to note that the comparison between trials is difficult due to the heterogeneous definition of pCR, it should be defined as the absence of invasive cancer in the breast and lymph nodes after completing neoadjuvant therapy (ypT0 /pN0), since other definitions of pCR have been used in the trials, generating pCR rates between 26% and 67%, with the peculiarity that the trastuzumab arms surpassed the arms that received chemotherapy alone.

CONCLUSION

Although the main weakness of this study is that it is a retrospective analysis, it is important to carry out this type of research to determine the reality of a cancer care center and be able to guide the treatment to a group of patients, in the institutions it reaches an acceptable percentage of rPC, however, a prospective analysis should be initiated, as well as proposing sequence-type chemotherapy, not concurrent, and dense doses, and not the standard dose, in this way to improve patient survival, as is the case with the data reported in the Cortazar meta-analysis. (14)

Finally, state policies should be sought in which Pertuzumab is incorporated into neoadjuvant treatment, select patients well and reach 60% response rates as demonstrated in the Neosphere and Tryphaena studies (15-20).

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