

Complete pathological response in patients with Her2 breast cancer treated with neoadjuvant therapy in the “Instituto de Cancerología Las Américas de Medellín” between 2007-2020.

Respuesta patológica completa en pacientes tratadas con neoadyuvancia y adenocarcinoma de seno que expresan receptores Her2 en el Instituto de Cancerología Las Américas de Medellín, en el periodo 2007-2020

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MESH: Neoadjuvant; Pathologic complete response; Pre-operative treatment; Residual disease.

Abstract

Introduction

Breast cancer represents the principal cause of death by cancer in women in Colombia. North American data report an improve in overall survival (OS) and disease-free survival (DFS) in recent years, comparing with results 10 years ago; These improvements are significant and maybe are in relation to better treatment strategies guided by immuno-histochemical sub-classification of the breast cancer. The role of the pathological response of the tumor to neoadjuvant therapy is an important tool, CTneoBC, showed improvements in DFS and OS in a patient with a complete pathological response in the breast and the axillae compared with patients with CPR only in the breast.

Methods

Retrospective analysis of the patient attended between 2007-2020 in the “Instituto de Cancerologia Las Americas, Auna”, with the diagnosis of non-metastatic breast cancer Her2+/Luminal B2 and that received neoadjuvant chemotherapy.

Results

Between 2007-2020, 467 patients were registered in the database. Mean age was 50 years, mean BMI was 26.9, the size of the lesion (in the pre neoadjuvant treatment evaluation) was 48mm, 29.6% presented without nodal involvement; 155 (32.3%) had ER and PR negative on IHC. Of the patients with the report of the proliferation index, 341 patients, 89% had a ki67>20%.

Grade 1&2 (OR 0,5 IC 0,37-0,81, p:0,03), ER + (OR 0,65 IC 0,43-0,97, p:0,04), PR + (OR 0,44 IC 0,37-0,81, p:0,03), were statistically associated with low PCR rates, whereas Her2 strong positivity (3+) was associated with high PCR rates (OR 3.3; IC 1,3-8,35; p:0,013) The average five year overall survival was 79.1% (IC 73.5-83.6) with a median 35 months of follow up. In the group who achieved CPR, one hundred eighty four (91.5%, CI 95% 82.6-95.9) patients were alive at 5 years, instead 73.6% (CI 66.4-79.6) in non CPR group.

Conclusions

In patients with breast cancer Her2+, grade 3, ER -, PR -, Her2 strong positivity (3+) and principally use of anti Her 2 neoadjuvant treatment was statistically associated with high PCR. Surgery window time was also associated with PCR rate. The PCR rate it's associated with better long term results like overall survival

Introduction

Breast cancer represents the principal leading cause of death by cancer in women in Colombia, with the highest incidence. It's estimated that each year thirteen thousand new cases are reported, and 3702 women's will die by this disease every year.(1–3)

Data from de Antioquia's population cancer registry identify that breast cancer represents 17% of the total cases of cancer in Antioquia, being the cancer with the highest prevalence during the last 3 years, and the second cause in mortality, only supered by lung cancer deaths, explaining the 13,5% mortality by cancer in the region(4–7).

North American data report an improved overall survival (OS) and disease-free survival (DFS) in recent years, comparing with results 10 years ago; These improvements are significant and maybe are

due to better treatment strategies guided by immuno-histochemical (IHC) sub-classification of breast cancer(8,9).

Using these markers, breast cancer could be divided into 4 subgroups. (10,11)

Luminal A: is characterized by the expression in the cell membrane of estrogen and progesterone receptors (ER, PR) without expressing human epidermic growth factor receptor 2 (HER2) and with a low proliferation index (ki67)

Luminal B1: are characterized by ER+, Her2-, and PR – or high Ki67.

Luminal B2: presents with ER+, Her2+, independent from RP or ki67 values.

Her 2 enrichment: this subgroup has Her2+ and ER-
Triple-negative (TNBC): are breast cancer with ER-, PR-, and Her2-.

Approximately 15% to 20% of breast cancers overexpress Her2.

The standard treatment in the USA and Europe is the administration of neoadjuvant chemotherapy or anti Her2 therapy in the following cases(12):

1. Locally advanced disease: patients with stage 3, or with T3 (JCCN 8th ed) independent of the IHQ subgroup.
2. Patients with >T1c TNBC or Her2+(13)
3. Patients with bad tumor/breast relation, with possible future breast-conserving surgery (BCS).

Benefits of neoadjuvant treatment in patients Her2+ are: increased the rate of BCS without compromising(14), and even, improving the oncologic long-term results like OS and distant recurrence(15,16).

Adding trastuzumab to neoadjuvant chemotherapy not only doubles complete pathological response (CPR) rates, but it is also associated with improved DFS(17)(18). The role of the pathological response of the tumor to neoadjuvant therapy is another important tool, in the combined analysis, CTneoBC, which included almost 12000 patients, the complete pathological response (CPR), in the breast and axillae, was associated with improvements in DFS and OS compared with patients with CPR only in the breast. This association was strong in TNBC and Her2 enrichment group, decreasing the probability of death in 84% and 71% respectively(19).

In Colombia, there have not been studies that analyze exclusive CPR after neoadjuvant therapy and its association with the different clinical variants. The objective of this study is precisely this one.

Methods

This is a retrospective analysis of the patient attended between 2007-2020 in the "Instituto de Cancerologia Las Americas, Auna", (Medellin, Colombia) with the diagnosis of non-metastatic breast cancer Her2+/Luminal B2 and that received neoadjuvant chemotherapy. Data were obtained from institutional cancer registry RIC REDCAP. Exclusion criteria are age<14 years, age>75 years, the presence of second primary cancer in the last 5 years (no melanoma skin cancer), <6 months expectation of life after start of neoadjuvant therapy and lost, in each patient, of 25% of the data.

We used the following PCR definition: the absence of tumor invasive component after neoadjuvant treatment in the breast and lymph nodes.

Quantitative variables were expressed like standard deviation (SD) or interquartile rank, Kolmogorov-Sminov test was used for corroborate normality. Categorical variables were expressed like absolute values or percentages. Differences in OS by de use of anti Her2 neoadjuvant chemotherapy were assessed using the Kaplan-Meier method and compared with log rank test. The test used by bi-variate analysis were Chi-square test, T student, U Mann Whitney and measures of associations were evaluated using OR. All analyses were conducted using STATA 12 software (Stata Corp, Tx, USA).

This project was conducted in accordance and approval with the "Instituto de cancerología las americas-AUNA" Ethics Board and with the 1964 Helsinki Declaration and its later amendments.

Results

Between 2007-2020, 467 patients were registered in the database. the characteristics are summarized in Table 1.

Average age was 50 years, mean BMI was 26.9, the average size of the lesion (in the pre neoadjuvant treatment evaluation) was 48mm, 29.1% presented without nodal involvement. 43.5% of patients had familiar history of breast cancer. The most common stage at presentation was stage III with 54.2% followed by stage II 34.9% and stage I with 7.5%.

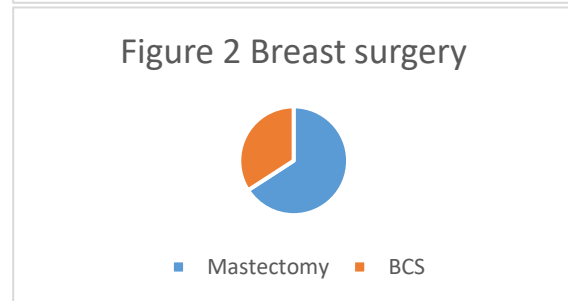
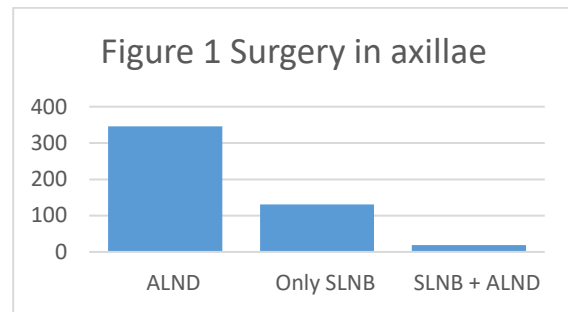
Figures 1 and 2 show the type of surgery offered for the patients. 69% had ALND, 131 patients SLND, 66% (328 patients) mastectomy and 34% BCS.

Table 2 shows the bi/multi variate analysis of PCR with the respective statistical results, Grade 1&2 (OR 0,55 IC 0,37-0,81, p:0,03), ER + (OR 0,65 IC 0,43-0,97, p:0,04), PR + (OR 0,44 IC 0,37-0,81, p:0,03),

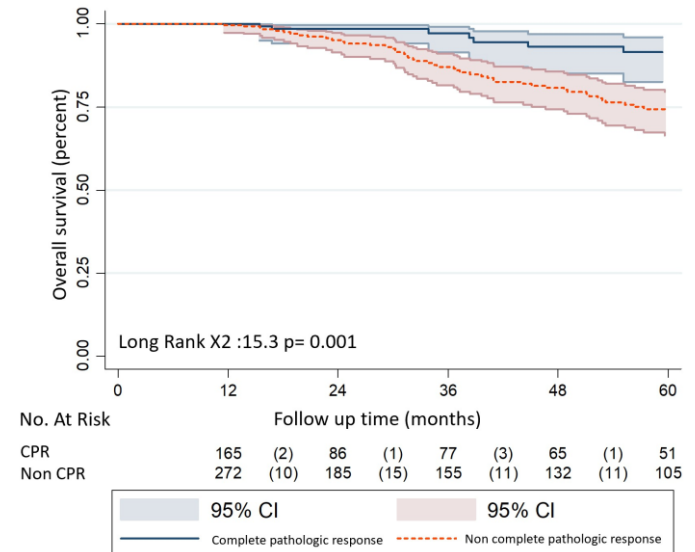
(+2 plus FISH+) were statistically associated with low PCR rates, whereas Her2 strong positivity (3+) was associated with high PCR rates (OR 3.3; IC 1,3-8,35; p:0,013). Surgery window time was related to PCR rates also.

Table 1

Characteristics	Result	Total 467 (%)
N		
Age, years		50
		22-75
Weight, Kg		65.7
		35-114
BMI		
<20		11 (24)
21-25		167 (35.8)
26-30		173 (37)
>30		113 (24.2)
T status		
T1		45 (9.6)
T2		173 (37)
T3		82 (17.6)
T4		166 (35.5)
N status		
N0		138 (29.6)
N1		241 (51.6)
N2		73 (15.6)
N3		9 (1.9)
Estrogen receptor		421
Positive		270 (64.1)
Negative		151 (35.9)
Progesterone receptor		418
Positive		232 (55.5)
Negative		186 (44.5)
HER- 2 IHC		378
3+		350 (92,6)
2+ (FISH+)		28 (7,4)
Ki67		342
<20		38 (11.1)
≥20		304 (88.8)
Histologic grade		459
I		44 (9.6)
II		163 (35.5)
III		252 (54.9)
Lymphovascular invasion		467
Yes		72 (15.4)
No		395 (84.6)
Complete pathological response		
Yes		184 (39)
No		283 (61)



The average five year overall survival was 79.1% (IC 73.5-83.6) with a median 35 months of follow up. In the group who achieved CPR, one hundred eighty four (91.5%, CI 95% 82.6-95.9) patients were alive at 5 years, instead 73.6% (CI 66.4-79.6) in non CPR group. (fig 3)



Ninety patients had initially, on biopsy, HER2 negative results, that were positive in the surgery specimen. 345 patients received neoadjuvant based chemotherapy and the other 26% received neoadjuvant treatment without anti Her 2 therapies, most of these patients were the 90 patients reported before (with Her2 negative on biopsy) and patients initially (first and second neoadjuvant chemotherapy cycles) treated in other institution different from AUNA.

None of the 467 patients received neoadjuvant radiotherapy.

The CPR rate was 3 times in patients with trastuzumab neoadjuvant treatment compared with those without it (fig 4)

Figure 4

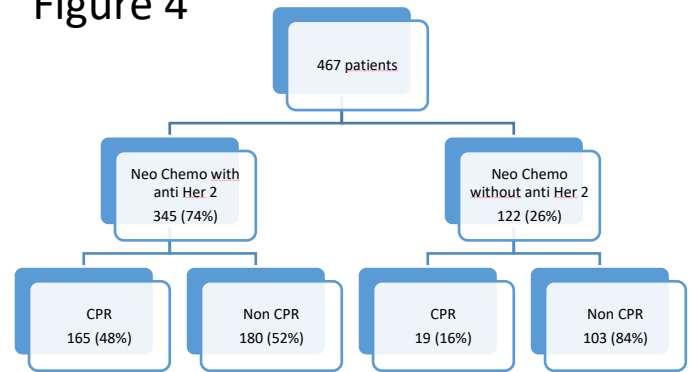


Table 2
Variable
Age
(years)

Variable	CPR (#)	Non CPR (#)	Total (#)	OR (IC)	p value
Age (years)					
<40	26	51	77	0.74 (0.44 -1.25)	0.32
>40	158	232	390		
Grade					
1&2	65	142	207	0.55 (0.37-0.81)	0.003
3	114	138	252		
Ki 67					
<20%	14	24	38	0.62 (0.31-1.25)	0.24
≥20%	147	157	304		
ER					
Pos	104	166	270	0.65 (0.43-0.97)	0.047
Neg	74	77	151		
PR					
Pos	79	153	232	0.44 (0.29-0.65)	0.0001
Neg	100	86	186		
Her2+					
3+	166	184	350	3.30 (1.30-8.35)	0.013
Fish	6	22	28		
Surgery window time (days)					
<15	7	10	17	1.00	0.04
16-45	70	91	161	0.91	
46-90	84	127	211	1.05	
91-180	21	31	52	1.03	
>180	0	12	12		

Discussion

In the present study, we used, the most common accepted (20,21) PCR definition: the absence of tumor invasive component after neoadjuvant treatment in the breast and lymph nodes.

In our population grade 3, ER -, PR -, Her2 strong positivity (3+) and principally use of anti her 2 neoadjuvant therapies were statistically associated with high PCR rates; surgery window time was

associated with PCR rate, and PCR rate was associated with an improvement in overall survival. These findings, are of greater importance in the region; it's known that the existence of non-recognized variable or non-measurables variables could impact the results between different region even using the same recommendations and protocols that are based on reports of populations different than ours, even though the data obtained in this paper, is according with data report in the universal literature, hence we reaffirmed some results previously reported. One of the most studied data regarding CPR, in patients with breast cancer luminal B2 or Her2 enrichment, is that to improve overall survival (primary goal) and PCR rate (surrogate result), it is required to block the Her2 receptor with a monoclonal antibody (trastuzumab)(22). Based on our results, we found a NNT=3 for PCR, using trastuzumab (16% to 48%), this finding was in correlation with data from the phase 3 trial NOAH(18) in which they found a 19% PCR rate using only neoadjuvant chemotherapy, and adding trastuzumab to this neoadjuvant treatment increased PCR rate to 38% (p:0.001, NNT 5), also in this trial, they reported a better DFS and OS5y adding trastuzumab to neoadjuvant chemotherapy. (63% to 74%; HR 0.66; p:0.055), these results was observed also in other studies; in a pooled analysis by Petrelli et al, they showed that adding trastuzumab to neoadjuvant chemotherapy decrease the relapse rate (20% to 12%) and increases the PCR rate from 20% to 43% (RR 2.07; CI 1.41-3.30 p=0.0002)(23); von Minckwitz et al demonstrated that adding trastuzumab to neo adjuvant chemotherapy in Her 2 + breast cancer patients was associated with 3.2 fold increased in PCR rate. (24)(25). In the pooled analysis of almost 6500(13) patients with breast cancer that received neoadjuvant treatment, and achieved PCR had better DFS (HR 0.446) compared with patient who not get PCR, and this correlation was bigger in patients with TNBC or Her2+ breast cancer(19). Also in the combined analysis, CTneoBC, which included almost 12000 patients, the complete pathological response (CPR), in the breast and axillae, was associated with improvements in DFS and OS compared with patients with CPR only in the breast. In the NeoSphere trial was reported DFS 5y of 75% in patients with non-CPR vs 85% in patients with CPR, after neoadjuvant dual blockade her2; results

that were confirmed by phase 2 TRYPHAENA that demonstrated the Her 2 dual blocking (trastuzumab+pertuzumab) was associated with an increase in PCR rates (from 55% to 64%) compared to neoadjuvant chemotherapy+trastuzumab alone (26,27); this effect was bigger in patients with ER-negative (27,28).

Untch et al, report in the TECHNO trial (33) and GEPARQUATTRO (34) that, using trastuzumab, PCR was associated with better OS and hormone receptors negativity.

Based on these results, recommendations from St. Gallen and ESMO (11,29) guidelines include neoadjuvant chemotherapy plus Her2 blockade, in patients with breast cancer Her2+. The trastuzumab must be used for 1 year more after the surgery (adjuvant treatment) and if the patient didn't achieve a PCR the use of emtansine must be considered, based on the result of the Katherine phase 3 trial (14) which compared 14 cycles of adjuvant T-DM1 with 14 cycles of trastuzumab in patients with residual invasive disease following neoadjuvant trastuzumab-based therapy, they found a reduced risk of invasive and distant recurrence and an increased invasive disease-free survival at 3 years from 77.0% to 88.3% (HR 0.50; P < .001). In patients with high-risk disease, ESMO and St. Gallen guidelines recommend using dual blockade Her 2 in form of neoadjuvant therapy and for 1 year in form of adjuvant therapy.

About 20% of the cohort was initially considered HER-2 negative on biopsy at diagnosis, which is considered a high number. There are historical reports that suggest a change of around 3% when compared with the definitive pathology 10 times lower than that reported in this work, which suggests possible technical problems in the interpretation of HER-2 initial and suggests the need for pathology review before initiating treatment by highly trained pathologists (32).

The disadvantages of this study are principally explained by the observational/analytical non-experimental character, also, we chosen PCR as primary outcome, but the definition of PCR and treatment of lymph node after neoadjuvant treatments is not universally equal. We decided to take PCR as the primary outcome because PCR has emerged as an early endpoint for clinical trials investigating novel approaches, decreasing the time to evaluate these agents, also because PCR it's a well known and well-studied surrogate for long-term outcomes. In a future analysis, we plan to report the association of the chemotherapeutics

Conflict of interest

Author D Gonzalez reports participation in advisory boards for Pfizer, Roche, Novartis, Lilly. All other others declare they have no conflicts of interest.

Conclusion

In patients with breast cancer Her2+, grade 3, ER -, PR -, Her2 strong positivity (3+) and principally use of anti Her 2 neoadjuvant treatment were statistically associated with high PCR. Surgery window time was related to PCR rate. The PCR rate it's also is associated with better long term results like overall survival.

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