Neoadjuvant chemotherapy impacts HER2 status as defined by Sataloff classification and consequent follow up in a lower middle-income country

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INTRODUCTION

In Algeria, breast cancer (BC) remains the most common and leading cause of cancer-related death for both sexes, accounting for 22.6% and 13.7% of cases, respectively (Globocan, 2022). BC is a heterogeneous disease, encompassing several molecular subtypes defined by two important prognostic and predictive biomarkers: hormone receptors (HR) and the HER2 oncoprotein. Three molecular subtypes are distinguished: luminal, HER2-enriched, and triple-negative. Different therapeutic options are applied in Algeria by combining surgery, radiotherapy, chemotherapy, hormone therapy, targeted therapies, and immunotherapy. Furthermore, neoadjuvant chemotherapy (NACT) followed by surgery remains the standard treatment in Algeria, primarily due to its affordability and wider availability compared to other methods. Unfortunately, one post-NADC limiting factor, tumor heterogeneity, can influence therapeutic response or lead to treatment resistance and a poor prognosis. Consequently, post-NADC heterogeneity is a significant concern, particularly if it affects HER2 tumor expression. The latter situation can be particularly problematic in Algerian public hospitals, where it exacerbates the shortage of healthcare products, such as anti-HER2 therapies. We therefore evaluated the evolution of HER2 status after NACT in response to different protocols offered to patients with BC.

MATERIALS & METHODS

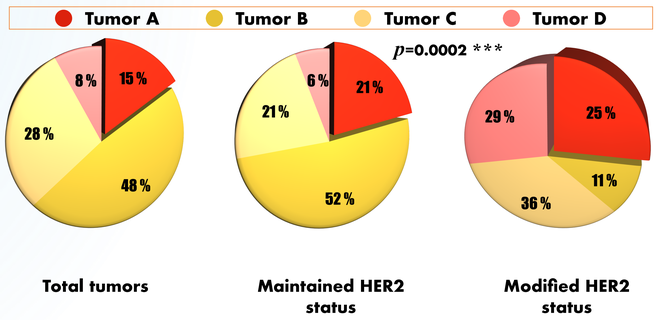
This single-institution, retrospective study analyzed 61 BC patients treated in 2024 at the Cancer Control Center, Annaba, Algeria. This study aimed to investigate changes in HER2 status, as determined by immunohistochemistry (IHC) before and after NACT in patients with BC, and to evaluate the impact of any modification on pathological complete response (pCR) according to the Sataloff classification. According to the guidelines, all patients received NACT, with or without anti-HER2 therapy (Trastuzumab with or without Pertuzumab). All patients underwent post-NCAT surgery, with a tumor biopsy performed before NCAT. Central assessment by IHC of HR, HER2 and Ki67 was performed and a threshold of>10% has been used for HR positivity. The percentage of patients with different clinicopathological parameters was compared using a Chi-square test. pCR was evaluated according to the Sataloff classification. Descriptive statistics, the Chi- square test or the Welch test were used to determine statistical differences.

RESULTS

Table 1 : Baseline demographics, clinical characteristics, and response after NACT for total and in regard to post-NACT-HER2 status.

	All N = 61	Maintained HER2 status N = 33	Modified HER2 Status N = 28	*p*-value
Age, years	50.02 (24-87)	51.70 (27-77)	48.04 (24-87)	0.6415
Laterlaty				
Left	22 (36,07%)	18 (18,03%)	16 (18,03%)	
Right	34 (55,74%)	11 (29,51%)	11 (26,23%)	0.8062
Bilateral	1 (1,64%)	1 (1,64%)	0 (0%)	
ND	4 (6,56%)	3 (4,92%)	1 (1,64%)	
NADC				
Anthracyclines free therapy	17 (27,87%)	9 (14,75%)	8 (13,11%)	0.1349
Anthracyclines-contained therapy	24 (72,113%)	24 (39,34%)	20 (32,78%)	
Pathological history				
Diabetes	5 (7,92%)	3 (2,97%)	3 (4,95%)	
Hypertension	7 (11,88%)	6 (1,98%)	6 (9,9%)	0.1019
Other	21 (34,65%)	9 (19,8%)	9 (14,85%)	
No history	22 (45,54%)	12 (20,79%)	12 (24,75%)	
Menopausal status				
Menopausal	21 (8,19%)	14 (26,92%)	9 (17,3%)	0.7805
Non-menopaual	29 (11,47%)	16 (30,76%)	13 (25%)	
Molecular status pre-post NADC				
Luminal A	22 (31,1%)-42 (76,36%)	12 (19,6%)-25 (45,4%)	10 (16,39%)-17 (30,9%)	0.1918
Luminal B	23 (16,38%)-8 (14,55%)	13 (21,31%)-5 (9,09%)	10 (16.39%)-3 (5,4%)	-
HER2-enriched	10 (32,78%)-3 (5,45%)	5 (8,19%)-2 (3,63%)	5 (8,19%)-1 (1,81%)	>0.999
Triple negatif	6 (19,66%)-2 (3,64%)	3 (4,91%)-1 (1,8%)	3 (4,91%)-1 (1,81%)	
Hormonal receptor status				
HR positif	48 (78,69%)	27 (44,26%)	21 (34,43%)	0.5471
HR negatif	13 (21,32%)	6 (9,84%)	7 (11,48%)	
preNACT HER2 Status				
HER2-0	18 (29,5%)	10 (16,39%)	8 (13,11%)	0.1485
HER2-Low	33 (54,1%)	15 (24,59%)	18 (29,51%)	
HER2-3+	10 (16,39%)	8 (13,11%)	2 (3,28%)	

Figure1 : Pie charts showing the distribution of pCR according to Staloff-T classification among total tumors (left), tumors with post-NCAT HER2-maitained status (middle) or post-NCAT HER2-modified status (left).



RESULTS

Figure2 : Comparison of pCR according to Sataloff-Tumor classification and for post-NCAT HER2-modified status.

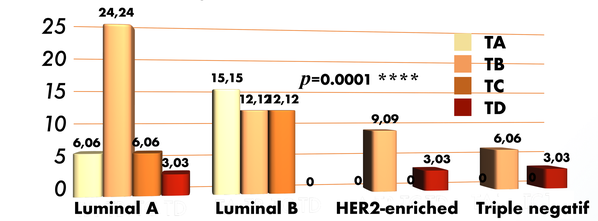


Figure3: Comparison of pCR according to Sataloff-Tumor classification and for post-NCAT HER2-modified status.

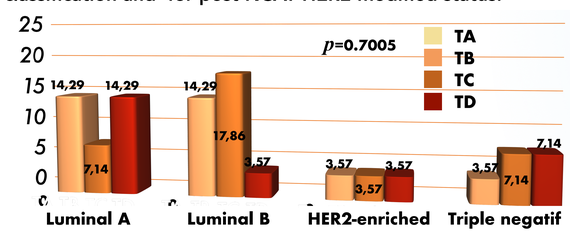
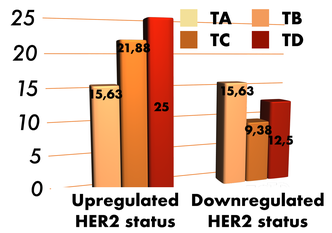


Figure4: Comparison of pCR according to Sataloff-Node classification for post-NCAT HER2-modified status.



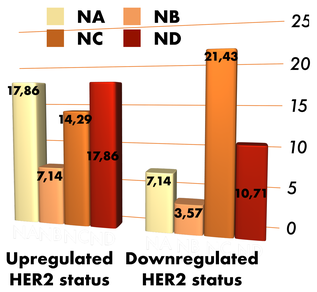


Figure5: Comparison of pCR according to Sataloff-Node classification for post-NCAT HER2-modified status.

DISCUSSION

In Algeria, NACT combined with surgery is recommended for BC patients. It represents a rapid and inexpensive systemic treatment option. However, postoperative tissue biomarkers can sometimes differ between samples explored before NACT and after surgery. In the present study, HER2 levels were altered in approximately half of the patients (48%), including increases (62%) or decreases (37%) in HER2 expression. This result is consistent with numerous studies reporting varying discrepancies between pre-NACT and post-treatment HER2 status (1). In our research, paired pre- and post-NACT samples primarily showed a gradual decrease (57%, 14%) from HER2-low to HER2-0 status or from HER2-3+ to HER2-low status. However, HER2 overexpression was randomly observed in 14% patients, with a transition from HER2-0 to HER2-Low or even to HER2-3+. Loss of HER2 positivity in residual tumor was associated with a worse prognosis than for tumors remaining HER2-positive after NACT treatment (2,3). In the present study, the pathological complete response rate (pCR) was assessed according to the Sataloff criteria and compared between tumors with maintained or altered HER2 status. A better pR was observed in tumors with maintained HER2 status and a predominant Sataloff category B (52%) compared with tumors with altered HER2 status (36%).

Furthermore, the proportion of tumors without therapeutic effect was lower in those with maintained HER2 status than in those with altered HER2 status (6% vs. 29%, respectively). Demographic, clinical, or pathological characteristics did not influence this variation. Our results show that a stable HER2 level is a favorable prognostic factor for breast cancer. These results reinforce the need to make the determination of residual disease molecular status systematic and by centralized IHC analysis.

CONCLUSION

Our results support the pre-existing characteristic of NACT consequences, which is the significant effect of NACT on HER2 status. This reflects a real issue for achieving a complete pR for patients and a deal for managing BC in our country. Indeed, we found for the first time that concomitant analysis of Sataloff classification and HER2 changes can represent an endpoint surrogate for treatment achievement after NACT in patients, with a favorable prognosis associated with HER2 upregulation. The assessment of HER2 after NCAT in combination with Sataloff response is a prerequisite for managing the follow-up of patients. Determination of characteristics that lead to changement of HER2 status of BC after NADC is crucial in order to refine the personalized therapeutic strategy for patients treatment; thus, more attention should be paid to the changes in HER2 status before and after NADC.

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