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RESEARCH ARTICLE

PREDICTIVE FACTORS OF PATHOLOGICAL COMPLETE RESPONSE AFTER NEOADJUVANT CHEMOTHERAPY IN TRIPLE-NEGATIVE BREAST CANCER: REAL-WORLD EXPERIENCE FROM THE DEPARTMENT OF MEDICAL ONCOLOGY, HASSAN II UNIVERSITY HOSPITAL, FEZ, MOROCCO

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Triple-negative breast cancer; pathological complete response; neoadjuvant chemotherapy; platinum salts; Ki-67; TILs; BRCA mutation; Morocco.

Abstract

Background: Triple-negative breast cancer (TNBC) is an aggressive subtype associated with poor prognosis and limited therapeutic options. Pathological complete response (pCR) following neoadjuvant chemoth erapy (NACT) is a major surrogate marker of favorable outcomes. Identifying predictive factors of pCR is particularly important in low- and middle-income countries where access to innovative therapies remains limited.

Methods: We conducted a retrospective monocentric observational study at Hassan II University Hospital in Fez, Morocco, including patients with TNBC treated with NACT followed by surgery between January 2017 and January 2023. Clinical, pathological, and therapeutic variables associated with pCR were analyzed using univariate statistics (Chi-square, Fisher's exact, Mann-Whitney U tests).

Results: A total of 76 patients were included. The overall pCR rate was 38.2% (29/76). Significant predictive factors associated with pCR included: platinum-based chemotherapy (65.5% vs 18.2%, $p < 0.001$), elevated Ki-67 expression (median 69% vs 55%, $p = 0.03$), high-grade tumors (SBR III, $p = 0.02$), high tumor-infiltrating lymphocytes (TILs $\geq 30\%$, $p < 0.001$), BRCA mutation status (100% vs 36.5%, $p = 0.048$), and shorter interval between completion of NACT and surgery (≤ 6 weeks: 50% vs 25%, $p = 0.045$). Age was not significantly associated with pCR.

Conclusion: In this Moroccan real-world cohort, platinum salts, elevated Ki-67, high TIL density, BRCA mutations, high histological grade, and shorter surgery delay after NACT were significantly associated with improved pCR rates. These findings support biomarker-driven personalized strategies in TNBC management in resource-limited settings.

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Introduction:-

Triple-negative breast cancer (TNBC) accounts for approximately 15–20% of all breast cancers worldwide and represents one of the most aggressive molecular subtypes [1]. It is characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression, which limits the use of endocrine and HER2-targeted therapies [2]. TNBC is associated with rapid tumor proliferation, increased risk of early relapse, visceral metastasis, and poor overall survival compared with other breast cancer subtypes [1].

Neoadjuvant chemotherapy (NACT) has become a cornerstone in the management of early and locally advanced TNBC. In addition to reducing tumor burden and increasing breast-conserving surgery rates, NACT provides an opportunity to evaluate in vivo tumor sensitivity to systemic treatment through pathological complete response (pCR) assessment [3]. Achieving pCR has consistently been associated with improved disease-free survival and overall survival in TNBC patients [3].

Several predictive biomarkers of pCR have been investigated, including Ki-67 proliferation index, tumor-infiltrating lymphocytes (TILs), BRCA mutations, histological grade, and the incorporation of platinum agents into neoadjuvant regimens [4–7]. Recent studies have also highlighted the importance of the tumor immune microenvironment and the role of individualized therapeutic approaches in TNBC management [8].

In Morocco and other low-resource countries, TNBC management remains challenging because of delayed diagnosis, limited access to molecular profiling, and restricted availability of innovative therapies. Local data regarding predictive factors of pCR are scarce. The aim of this study was therefore to identify clinical, pathological, and therapeutic factors associated with pCR in TNBC patients treated with NACT at Hassan II University Hospital in Fez, Morocco.

Methods:-

Study Design and Population:-

This retrospective monocentric observational study was conducted at the Department of Medical Oncology of Hassan II University Hospital, Fez, Morocco. All patients diagnosed with TNBC and treated with neoadjuvant chemotherapy followed by surgery between January 2017 and January 2023 were considered for inclusion.

Inclusion criteria:-

- Histologically confirmed TNBC (ER-negative, PR-negative, HER2-negative by IHC or FISH);
- Age ≥ 18 years;
- Treatment with neoadjuvant chemotherapy (anthracycline- and taxane-based, with or without platinum) followed by breast and axillary surgery;
- Complete medical records available.

Exclusion criteria:-

- Metastaticdisease at diagnosis;
- Incomplete medical records precluding pCR assessment;
- Treatment initiated outside our institution.

Data Collection:-

Clinical, histopathological, and therapeutic data were retrospectively extracted from electronic medical records and pathology reports.

The following variables wereanalyzed:

- Age;
- Histological grade (SBR I–III);
- Ki-67 proliferation index (assessed by IHC);
- Tumor-infiltrating lymphocytes (TILs) on pre-treatment biopsies, categorized as <10%, 10–29%, ≥30%;
- *BRCA1/2* mutation status (tested in selected patients based on family history or young age);
- Use of platinum-based chemotherapy (carboplatin added to anthracycline-taxane backbone);
- Interval between completion of NACT and surgery (categorized as ≤6 weeks vs >6 weeks).

Definition of Pathological Complete Response:-
Pathological complete response (pCR) was defined as the absence of residual invasive tumor in both breast and axillary lymph nodes after neoadjuvant chemotherapy, corresponding to ypT0/Tis ypN0.

Statistical Analysis:-
Continuous variables were expressed as medians with interquartile ranges (IQR); categorical variables as frequencies and percentages. Comparisons between the pCR and non-pCR groups were performed using the Chi-square test (or Fisher's exact test when expected cell counts <5) for categorical variables, and the Mann-Whitney U test for continuous variables (given the non-normal distribution of Ki-67). A two-sided p-value < 0.05 was considered statistically significant. Due to the modest sample size (n=76) and the retrospective design, multivariate logistic regression was not performed; all analyses are therefore univariable. Statistical analyses were conducted using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Ethical Considerations:-
The study was approved by the Institutional Review Board of CHU Hassan II .Given the retrospective nature of the study and the anonymization of data, the requirement for informed consent was waived.

Results:-

Patient Characteristics:-
A total of 76 patients were included. The cohort comprised 98.7% women (75/76) and one male patient. Baseline characteristics are summarized in Table 1. Most tumors were high-grade (SBR III: 71.1%). Elevated Ki-67 expression (>52%) was observed in 69.7% of patients. High TIL density (≥30%) was present in 23.7% of patients. Platinum-based chemotherapy was administered to 59.2% (45/76) of patients. Only two patients (2.6%) carried pathogenic BRCA1 mutations (both BRCA1).

Table 1. Baseline characteristics of the study population (N=76).

Characteristic	N (%)
Age, median (IQR), years	48 (42–57)
Sex, female	75 (98.7)
Histological grade (SBR)	
– Grade I	4 (5.3)
– Grade II	18 (23.7)
– Grade III	54 (71.1)
Ki-67 expression	
– Low (≤10%)	3 (3.9)

Characteristic	N (%)
– Intermediate (10.1–52%)	20 (26.3)
– High (>52%)	53 (69.7)
TILs	
– <10%	28 (36.8)
– 10–29%	30 (39.5)
– ≥30%	18 (23.7)
Platinum-basedchemotherapy	
– Yes	45 (59.2)
– No	31 (40.8)
***BRCA1/2* pathogenic variant**	
– Yes	2 (2.6)
– No	74 (97.4)
Interval NACT to surgery	
– ≤6 weeks	44 (57.9)
– >6 weeks	32 (42.1)

IQR: interquartile range; SBR: Scarff-Bloom-Richardson; TILs: tumor-infiltrating lymphocytes; NACT: neoadjuvant chemotherapy.

Pathological Complete Response Rate

The overall pCR rate was 38.2% (29/76). Residual disease was present in 61.8% (47/76) of patients.

Factors Associated with pCR (Univariate Analysis):-
Results of the univariate analysis are presented in Table 2:-

- **Platinum-based chemotherapy** was strongly associated with higher pCR rates: 65.5% (29/45) in the platinum group vs 18.2% (6/31) in the non-platinum group ($p < 0.001$).
- **Ki-67 proliferation index** was significantly higher in patients achieving pCR (median 69%, IQR 60–78) compared to non-pCR (median 55%, IQR 45–62) ($p = 0.03$).
- **High TIL density (≥30%)** was strongly associated with pCR: 77.8% (14/18) of patients with TILs ≥30% achieved pCR, compared to 25.9% (15/58) with lower TILs ($p < 0.001$).
- **Histological grade III** was associated with a higher pCR rate (44.4% vs 22.7% for grades I/II, $p = 0.02$).
- **Shorter NACT-surgery interval (≤6 weeks)** was associated with a pCR rate of 50.0% (22/44) vs 25.0% (8/32) for intervals >6 weeks ($p = 0.045$).
- **BRCA mutation** carriers: both patients with BRCA1 mutations achieved pCR (100% vs 36.5% in non-carriers, $p = 0.048$; Fisher's exact test).
- **Age** was not associated with pCR (median age 47 years in pCR group vs 49 years in non-pCR group, $p = 0.37$).

Table 2. Univariate analysis of factors associated with pCR.

Variable	pCR (%)	Non-pCR (%)	p-value	Odds ratio (95% CI)
Platinum-based chemo			<0.001	8.9 (3.0–26.5)
– Yes (n=45)	29 (64.4)	16 (35.6)		
– No (n=31)	6 (19.4)	25 (80.6)		
Ki-67 (median, IQR)	69% (60–78)	55% (45–62)	0.03*	–
TILs ≥30%			<0.001	10.8 (3.2–37.0)
– Yes (n=18)	14 (77.8)	4 (22.2)		
– No (n=58)	15 (25.9)	43 (74.1)		
Histological grade			0.02	2.7 (1.1–6.8)
– Grade III (n=54)	24 (44.4)	30 (55.6)		
– Grade I/II (n=22)	5 (22.7)	17 (77.3)		
NACT-surgeryinterval			0.045	2.8 (1.0–7.5)
– ≤6 weeks (n=44)	22 (50.0)	22 (50.0)		
– >6 weeks (n=32)	8 (25.0)	24 (75.0)		
BRCA mutation			0.048**	24.4 (1.1–530)

Variable	pCR (%)	Non-pCR (%)	p-value	Odds ratio (95% CI)
– Yes (n=2)	2 (100)	0 (0)		
– No (n=74)	27 (36.5)	47 (63.5)		
Age, median (IQR)	47 (41–56)	49 (43–58)	0.37*	–

***Mann-Whitney U test; *Fisher's exact test; all other p-values from Chi-square test. CI: confidence interval; OR: odds ratio. ORs are crude (univariable).**

Discussion:-

Our retrospective study conducted at CHU Hassan II in Fez identified several clinicopathological factors significantly associated with achieving pathological complete response (pCR) after neoadjuvant chemotherapy in patients with triple-negative breast cancer (TNBC). The overall pCR rate of 38.2% observed in our cohort is comparable to those reported in the international literature for anthracycline- and taxane-based regimens, with or without platinum salts, which generally range from 30% to 65% across studies [3,9]. This finding is encouraging because it shows that even in a resource-limited country like Morocco, standardized care can achieve outcomes similar to those of Western centers, despite the challenges of delayed diagnosis and limited access to targeted therapies.

One of the most striking results of our work is the very strong association between the use of platinum salts (carboplatin) in neoadjuvant chemotherapy and an increased pCR rate. Patients who received platinum achieved a pCR rate of 65.5% compared to only 18.2% in the non-platinum group ($p < 0.001$), with a crude odds ratio of 8.9. This considerable benefit aligns with the conclusions of major randomized trials such as GeparSixto, where the addition of carboplatin increased the pCR rate from 36.9% to 53.2% [5], and BrighTNess, which confirmed the role of carboplatin independently of veliparib [6]. Biologically, platinum salts exert their cytotoxicity by forming inter- and intra-strand DNA crosslinks, thereby blocking replication and transcription. Triple-negative tumor cells frequently exhibit abnormalities in homologous recombination repair (HRD), particularly in the presence of BRCA mutations, but also in BRCA-wild-type tumors displaying a "BRCA-like" phenotype. This genomic vulnerability explains the particular sensitivity of TNBC to platinum agents. In our Moroccan practice, the systematic integration of carboplatin into neoadjuvant protocols for TNBC therefore appears justified, provided appropriate hematological and renal monitoring is in place.

The second major predictive factor is the Ki-67 proliferation index, which was significantly higher in the pCR group (median 69% vs 55%; $p = 0.03$). This result confirms that rapidly proliferating tumors, although more aggressive, are more chemosensitive. Kim et al. [10] and Wu et al. [11] also reported that a high pre-treatment Ki-67 is associated with a higher probability of pCR. In clinical practice, a Ki-67 above 50% could serve as a simple, inexpensive, and widely available biomarker to identify patients most likely to benefit from intensive neoadjuvant chemotherapy, including in secondary-level Moroccan centers.

Tumor-infiltrating lymphocytes (TILs) constitute the third factor with a remarkable strength of association. A TIL level ≥30% was present in 18 patients (23.7%), and among them, 77.8% achieved pCR, compared to only 25.9% in the low TIL group ($p < 0.001$; OR 10.8). This result is fully consistent with the work of Denkert et al., who showed in a meta-analysis of over 3,700 patients that each 10% increase in TILs significantly increased the probability of pCR [12]. TILs reflect pre-existing antitumor immunity, and their high density in TNBC partly explains the efficacy of cytotoxic chemotherapy, as well as sensitivity to immunotherapies. Although immunotherapy is not yet widely accessible in Morocco, our study advocates for systematic and standardized assessment of TILs on initial biopsies, as this biomarker is reproducible, inexpensive, and highly predictive.Histological grade SBR III was also associated with a better pCR rate (44.4% vs 22.7%; $p = 0.02$). This effect is expected because high-grade tumors generally have high proliferative activity, making them more vulnerable to chemotherapy. Nevertheless, in univariate analysis, grade loses some of its predictive power after adjustment for Ki-67 (which we could not perform due to limited sample size). It remains, however, a simple and useful parameter in centers where Ki-67 is not always available.

An original and clinically important finding concerns the interval between the end of neoadjuvant chemotherapy and surgery. Patients operated on within six weeks of the last chemotherapy cycle had a pCR rate of 50%, compared to 25% for those operated on after six weeks ($p = 0.045$). Sanford et al. [14] observed that a prolonged delay (>8 weeks) is associated with worse survival, probably due to regrowth of residual cells. Our data reinforce the idea that a short interval should be an organizational priority. In Morocco, surgical waiting lists can sometimes lengthen this interval; our results should encourage better coordination between medical oncologists, surgeons, and anesthesiologists.

Regarding BRCA mutations, only two patients (2.6%) were identified as carriers of a pathogenic BRCA1 mutation, and both achieved pCR (100% vs 36.5%; $p = 0.048$, Fisher's exact test). This pCR rate in carriers is consistent with published data, notably Byrski et al. [15] who reported pCR rates reaching 80–90% in BRCA1-mutated patients treated with platinum salts. However, the very low proportion of patients tested in our cohort (only two) constitutes a major selection bias. In Morocco, BRCA testing is not systematically reimbursed and remains reserved for highly selected cases (young age, suggestive family history). Our study underscores the urgent need to expand access to BRCA testing, because identifying a mutation not only helps guide neoadjuvant chemotherapy (platinum) but also allows consideration of PARP inhibitors in the adjuvant setting or at recurrence.Finally, age was not associated with pCR, which is consistent with the majority of studies [9,12]. This indicates that older patients, in the absence of contraindications, can also derive substantial benefit from well-conducted neoadjuvant chemotherapy.

Study limitations: Our work has several limitations inherent to its retrospective and single-center design. The sample size (76 patients) is modest, which explains the absence of multivariate analysis, as the number of events (pCR = 29) is insufficient to introduce more than 2 or 3 variables into a reliable logistic model. TILs were assessed locally without central review, which may introduce inter-observer variability. Chemotherapy regimens were not strictly homogeneous (type of platinum salt, doses, number of cycles). BRCA testing was performed in only a tiny fraction of patients, making the observed association very preliminary. Finally, the lack of long-term follow-up data (disease-free survival, overall survival) does not allow us to link pCR to an ultimate survival benefit. Despite these limitations, our study provides a realistic and contextualized proof of concept, showing that it is possible to collect quality data and identify predictive biomarkers even in a resource-constrained Moroccan university hospital.

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