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ORIGINAL ARTICLE

Real-world experience of neoadjuvant chemotherapy for early breast cancer patients: an observational non-interventional study in Thessaloniki, Greece

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Summary

Purpose: *Neoadjuvant chemotherapy has been increasingly used in early-stage breast cancer. The results of large randomized clinical trials suggest the need for the wider use of preoperative therapy as it can result in a more conservative surgery, and can guide physicians to a more individualized approach in the adjuvant setting.*

Methods: *We aimed to analyze the outcomes of 203 patients with early-stage breast cancer who had received neoadjuvant chemotherapy at our institutions.*

Results and Conclusion: *Pathological complete responses (pCR) were obtained in 42.4% of all patients, with the highest percentage in hormonal receptor (HR)-negative and human epidermal growth factor receptor-2 (HER2)-positive cancers. Conversion of a clinically and/or cytologically node-positive to node-negative disease was achieved in 55.8% of patients. Patients who achieved a pCR had a significantly better outcome in terms of disease-free and distant disease-free survival. Patients with residual disease experienced a worse prognosis if they had HR-negative cancer compared to HR-positive patients for whom the use of adjuvant endocrine treatment likely led to better outcomes. These results are encouraging as they show that outcomes from large randomized clinical trials can be reproduced in the everyday clinical setting. Neoadjuvant chemotherapy may be the treatment of choice for HR-negative and/or HER2-positive early breast cancer patients. This may also be the case for the majority of HR-positive and HER2-negative patients with either locally advanced disease or disease extending to the axillary lymph nodes, as it may result in more conservative surgical interventions with fewer post-operative complications*

Key words: *eribulin, breast cancer neoadjuvant chemotherapy*

Introduction

Neoadjuvant chemotherapy (NAC), defined as the use of systemic cytotoxic therapy administered prior to definitive surgery, was historically reserved to reduce the size and extent of locally advanced or inoperable breast tumors [1]. However, NAC is currently used more widely in patients with early-stage disease. It results not only in higher rates of breast-conserving surgery and better resectability, but in higher rates of more conservative surgical approaches to the axilla, as sentinel lymph node biopsy (SLNB) or targeted axillary dissection (TAD) [2] can safely be performed. There is an increasing body of evidence showing that pathological complete response (pCR) after NAC is associated with a good prognosis, at least in specific subgroups, for example triple-negative and human epidermal growth factor receptor-2 (HER2)-positive subgroups [3]. Furthermore, it may serve as a rapid assessment of *in vivo* chemosensitivity, and could expedite the development and approval of treat-

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ments in breast cancer following the publication by the US Food and Drug Administration (FDA) of a new set of guidelines [4,5].

Understanding real-world treatment patterns, patient characteristics and outcomes is an important addition to large randomized controlled trials (RCTs). Patients treated in clinical practice will often be clinically distinct from patients included in RCTs, and it is encouraging to see how new data from RCTs can be reproduced in everyday clinical practice. Carefully selected and analyzed data from "real-world" evidence can, therefore, be useful as additional knowledge outside large, frequently industry-driven, or industry-sponsored trials [6,7].

Methods

We retrospectively collected data from the medical records of patients treated at our institutions between 2008 and 2018. All patients who had received NAC were included in the analysis. The age of the patients with a histologically confirmed diagnosis of breast cancer ranged from 18 to 85 years. All patients had pre-treatment core-needle biopsy with immunohistochemical determination of at least estrogen and progesterone receptors, as well as HER2. Since 2014, Ki67 expression has also been estimated in the pre-treatment biopsy as a standard of care. We included all patients for whom we had full histology reports from the final surgery on the day of the database lock.

There has been an evolution in the treatment of the axilla in NAC patients; however, not all patients in this report were treated with axillary lymph node dissection (ALND). Clinically node-negative patients (cN0), either pre- or post-NAC, underwent ALND until April 2012. Thereafter, all cN0 patients underwent a sentinel lymph node biopsy (SLNB) [8,9] and, where sentinel lymph nodes were positive, the patients subsequently underwent ALND. Clinically node-positive (cN1-2) patients underwent ALND until September 2015. Thereafter, targeted axillary dissection was performed. Briefly, the positive and/or suspicious lymph nodes were marked pre-NAC with carbon suspension tattoos [10] and, at the time of definitive surgery, they were removed together with the sentinel lymph nodes. In case of residual disease in the axilla, patients underwent ALND.

The primary endpoints of this study were the determination of pCRs in patients receiving NAC, and disease-free survival (DFS), defined as the time that elapsed between definitive surgery and first documentation of any cancer event (local or distant relapse of breast cancer, or any new cancer primary), or death. pCR was defined, according to the FDA guidelines [11], as no evidence of invasive disease in the breast or in the axillary lymph nodes (ypT0/Tis ypN0).

Statistics

Continuous variables were summarized with the use of descriptive statistical measures, namely, mean value, standard deviation, median, and range (minimum, maximum), and categorical variables were displayed as frequency tables. Chi-square (x^2) test was used to correlate the pCR rates with clinicopathological features of the disease. The Kaplan-Meier method was used to estimate the median DFS. Log-rank test was used to test differences of survival functions across groups. All data were collected from March to June, 2018 (database lock). According to the methodological features of an observational non-interventional study, all analyses were descriptive, and the results presented should be interpreted as such. All statistical analyses were performed using GraphPad Prism 8.0.1 software.

Results

Between 2008 and 2018, we identified 203 patients who had received NAC and had undergone surgery. The average age of the patients was 48.3 years, and most patients (n=192) presented with a ductal histology (infiltrative ductal carcinoma, [IDC]), while 12 patients had either infiltrative lobular carcinoma, mixed ductal and lobular carcinoma, or other histologies. Most patients received an anthracycline and taxane-based regimen. All HER2-positive patients received trastuzumab in combination with a taxane regimen (the majority after four cycles of an anthracycline-containing regimen) and continued trastuzumab for a one-year period. Since the approval of pertuzumab in the neoadjuvant setting, all HER2-positive patients received neoadjuvant pertuzumab with trastuzumab (Table 1).

Table 2 summarizes the response data and the population subgroups. pCR was observed in 86 (42.4%) patients, and there were 127 patients with no evidence of disease in the axilla (pN0). Of 138 patients with clinical, radiological, and/or cytological evidence of axillary disease pre-NAC, 77 (55.8%) patients were node-negative on the day of surgery. The rate of conversion from clinically node-positive to pathologically node-negative was higher in triple-negative (76.9%) and in HR-negative and HER2-positive patients (92.3%) (Table 3).

Ductal histology, lack of expression of hormonal receptors (HR), and HER2 overexpression

Table 1. Chemotherapy data

Chemotherapy	*n*
Anthracycline-containing regimen	183
Anthracyclines and taxanes	178
Taxanes without anthracyclines	10
Unknown	11
Addition of bevacizumab	6
Total	203

Table 2. Complete pathological response (pCR) according to staging, histology, hormonal receptors (HR), HER2, and genetic profile

		n	*pCR*	*p value*
Histology				0.0139
IDC		191	85 (44.5%)	
ILC/mixed/other		12	1 (9.1%)	
Hormonal receptors				< 0.0001
HR+ve		121	33 (27.3%)	
HR-ve		82	53 (64.6%)	
HER2 by ICH and/or FISH				< 0.0001
HER2+ve		77	52 (67.5%)	
HER2-ve		126	34 (27.0%)	
Subtype				< 0.0001
HR-ve	HER2+ve	36	29 (80.6%)	
HR-ve	HER2-ve	46	24 (52.2%)	
HR+ve	HER2+ve	41	23 (56.1%)	
HR+ve	HER2-ve	80	10 (12.5%)	
Grade (IDC only)				0.0199
Grade 1		4	2 (50%)	
Grade 2		57	17 (29.8%)	
Grade 3		129	67 (51.9%)	
Unknown		1	0 (0%)	
Ki67				0.0268
0-20		27	6 (22.2%)	
>20		151	68 (45.0%)	
Unknown		25	12 (48.0%)	
Clinical T-stage (pre-NAC)	HR-ve			0.0010
T1	62.5%	24	17 (70.8%)	
T2	42.7%	103	48 (46.6%)	
T3	36.1%	36	10 (27.8%)	
T4	20.0%	30	7 (23.3%)	
Tx		10	4 (40.0%)	
Clinical N-stage (pre-NAC)	HR-ve			0.2295
N0	52.8%	53	27 (50.9%)	
N+ve	37.7%	138	57 (41.3%)	
Nx		12	2 (16.7%)	
Genetic profile				0.0266
Unchecked		142	53 (37.1%)	
Checked		61	33 (54.1%)	0.0261
Wild-type		37	18 (48.6%)	
Any pathogenic mutation		16	11 (68.8%)	0.0135
BRCA1 or *BRCA2* pathogenic mutations		10	8 (80.0%)	
Other pathogenic mutations		6	3 (50.0%)	
Variants of unknown significance		8	4 (50.0%)	
Total		203	86 (42.4%)	

Table 3. No evidence of disease in the axilla (pN0) according to clinical (pre-NAC) stage, and conversion from clinically node-positive to pathologically node-negative, according to immunohistochemical type

Clinical Stage (cN)		*pN0*	*Conversion from clinically node-positive to pathologically node-negative*				
			Total	*HR-/HER2+*	*HR-/HER2-*	*HR+/HER2+*	*HR+/HER2-*
N0	53	45					
N+	138	77	55.8%	92.3%	76.9%	34.6%	16.7%
Nx	12	5					
Total	203	127					

were all statistically significantly related to pCR. The highest pCR rate was observed in patients with HR-negative and HER2-positive tumors (80.6%), of which all were of ductal histology. Lobular or mixed lobular and ductal cancers, and expression of HR in the absence of HER2, were all inversely related to pCR. However, as the majority of lobular cancers were HR-positive, this was not statistically significant due to the small number when we adjusted for HR (p=0.71). Grade IDC tumors had a statistically significant effect on pCR, with a higher rate of pCR in grade 3 (51.9%) than in grade 2 tumors (29.8%). A higher (>20%) expression of the Ki67 proliferation antigen led similarly to a higher pCR rate (45.3 vs 22.2%, p=0.02903).

Pre-treatment tumor (T)-size without node (N)-involvement was statistically significantly associated with pCR, as T1 tumors had a 70.8% chance of achieving a pCR vs. a 23.3% chance in T4 tumors. However, smaller tumors were more often HR-negative (62.5% in T1 vs 20.0% in T4), suggesting that clinicians were more likely to undertake NAC for small tumors if they were HR-negative. However, HR-positive patients were referred for NAC with more conventional criteria (large or clinically node-positive tumors).

A younger age, triple-negative disease, and a hereditary history of cancer in first and/or second-degree relatives were major factors associated with patients proceeding to undergo a genetic test. Germline mutation testing was performed in 63 patients (27 with triple-negative disease), with an average age of 41.4 years. Ten patients were diagnosed with a *BRCA1* or *BRCA2* mutation, while 6 more patients were diagnosed with a non-BRCA pathogenic mutation (one with *BRIP1*, two with *CHK2*, one with *TP53*, one with *PALB2,* and one with *RAD51B* mutations).

The presence of a pathogenic mutation was associated with a higher chance of achieving a pCR (68.8% for any mutation (p=0.0261), and 80% for *BRCA1/2* mutations (p=0.0135)).

In 6 tumors, the post-NAC tumor had a different immunohistochemical profile than those obtained through core biopsy at the time of diagnosis; four HR-positive and HER2-positive tumors had lost HER2 expression, one HR-positive and HER2-negative tumor had gained HER2 expression, and one tumor expressing low levels of HR was reported to be HR-negative in the final histology.

With a median follow-up of 1.69 years, there were 25 [%?] relapses, comprising 6 locoregional breast/lymph nodes, 2 contralateral breast cancers, one new ovarian cancer, and 16 distant relapses (metastatic breast cancer).

Median disease-free survival (DFS) for the whole population (defined as the time from definitive surgery to the day of relapse or last disease-free follow-up) was 8.55 years (Figure 1). Median distant-disease-free-survival was not reached (Figure 2). The response to NAC was a strong predictor for DFS (Figure 3). Median DFS for patients with pCR was not reached, while the median DFS

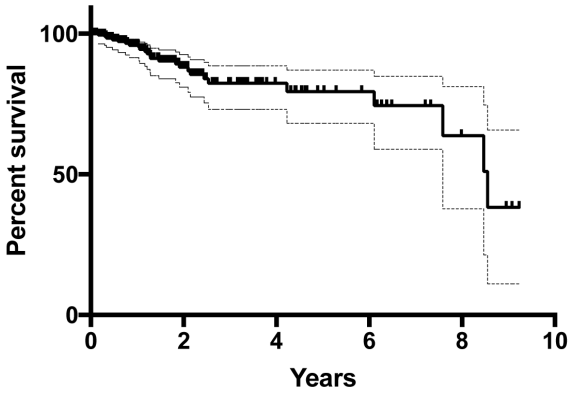

Figure 1. Disease-free survival (n=203). Thin lines represent 95% confidence intervals.

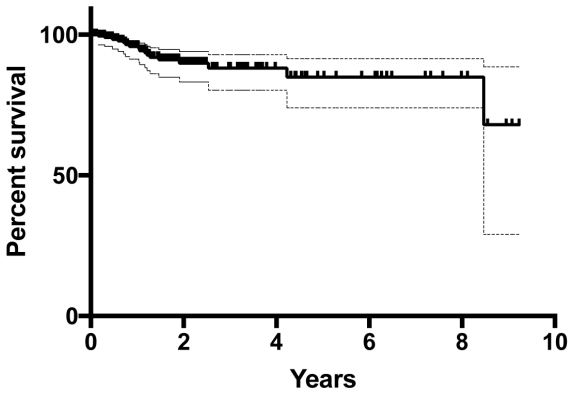

Figure 2. Distant disease-free survival (DDFS) (n=203). Thin lines represent 95% confidence intervals.

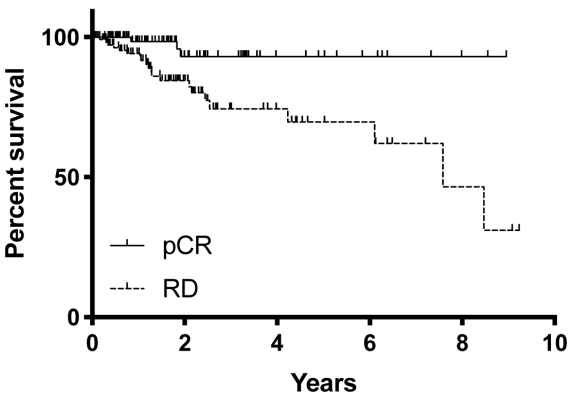

Figure 3. Disease-free survival according to the response to neoadjuvant chemotherapy (NAC). HR: 0.1842, 95% CI 0.08226-0.4129, p=0.002. DFS: disease-free survival, pCR: pathological complete response, RD: residual disease, HR: hazard ratio, CI: confidence interval.

was 7.58 years for patients with residual disease (hazard ratio (HR)=0.1843, 95% confidence interval (CI) 0.08226-0.4129, p=0.0021, using Log-rank test. The response to NAC was also a strong predictor for distant-DFS (Figure 4) (HR=0.1758, 95% CI 0.06731-0.4595, p=0.009, using Log-rank test). This was more evident in patients with HR-negative disease (HR=0.1088, 95% CI 0.03327-0.3556, p=0.0005, using Log-rank test) than in HR-positive disease (HR=0.1658, 95% CI 0.05078-0.5411, p=0.0485, using Log-rank test).

Finally, patients with residual disease post-NAC had a better prognosis if their tumors expressed estrogen and/or progesterone hormone receptors (Figure 5), with a median DFS of 8.47 vs 7.58 years for HR-negative patients, respectively, [HR=2.915, 95% CI 1.067-7.96, p=0.0094, using Log-rank test.

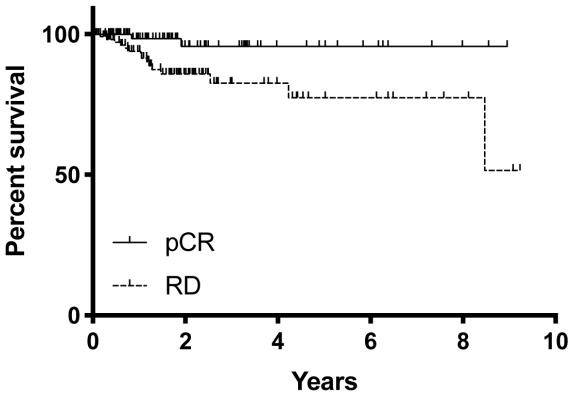

Figure 4. Distant disease-free survival (DDFS) according to the response to neoadjuvant chemotherapy (NAC). HR=0.9758, 95% CI 0.0673-0.4595, p=0.009. DDFS: distant disease-free survival, NAC: neoadjuvant chemotherapy, pCR: pathological complete response, RD: residual disease, HR: hazard ratio, CI: confidence interval.

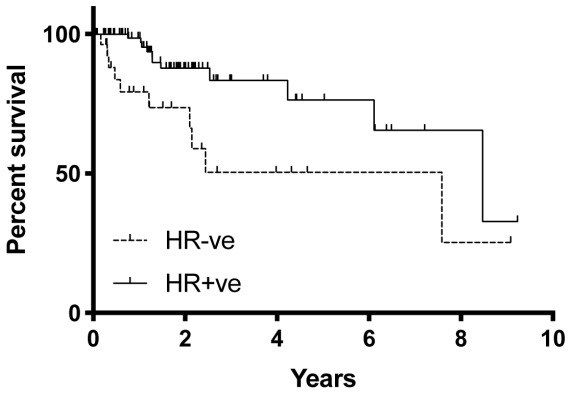

Figure 5. Disease-free survival according to hormone receptors in patients with residual disease after neoadjuvant chemotherapy. HR=2915, 95% CI 1.067-7.96, p=0.0094. HR-ve: no expression of estrogen or progesterone receptors, HR+ve: expression of estrogen and/or progesterone receptors, HR: hazard ratio, CI: confidence interval.

Discussion

Neoadjuvant chemotherapy is increasingly becoming the preferred standard of care in patients presenting with aggressive tumor histology or who need down-staging for an optimal surgical outcome.

As SLNB and targeted axillary dissection have proven to be safe and may spare patients from ALND [12] (which may increase the rates of post-treatment lymphedema), more patients are being referred for NAC. The high rate of conversion from node-positive to node-negative supports the use of NAC in node-positive patients with a favorable response receptor profile. Historically, two trials that tested the neoadjuvant vs the adjuvant approaches showed significantly lower nodal positivity with NAC. In the NSABP-B18 [13] and NSABP-B27 [14] trials, there was a significant reduction in node-positive disease in women undergoing NAC (33 vs 48%, p<0.001, and 40 vs 49%, p<0.001), clearly suggesting NAC's role in decreasing the axillary positivity. As more recent studies have led to the use of less-aggressive axillary surgery following NAC [15], the use of NAC to convert patients from being clinically node-positive to pathologically node-negative to avoid axillary clearance has become more widespread, resulting in the recent publication of guidelines for the management of axilla in clinical trials with a pCR endpoint [16]. In our database, the conversion of clinically, radiologically, and/or cytologically node-positive to pathological node-negative was 55.8%, a percentage that was higher in HR-negative histologies. Our study population was not a selected population from a clinical trial but comprised patients from everyday practice. This emphasizes the need for applying such guidelines in breast centers, with an intention to a more judicious use of ALND, to minimize morbidity from surgery.

Pathogenic mutations in genes that predispose to homologous recombination deficiency (HRD) have been related to response to NAC [17]. A better outcome concerning *BRCA1/2* mutated patients to NAC was first reported in 2002 [18], and has been confirmed in more recent studies regarding patients with triple-negative breast cancer [19,20]. In our series, pathogenic mutations in *BRCA1/2* genes were strongly predictive for pCR.

High-grade, HR-negativity, HER2-positivity, and a high Ki67 status were all associated with pCR. pCR was shown to be a strong prognostic factor for DFS, both in our study and in larger series. In both the NSABP B-18 [21] and NSABP B-27 [22] trials, pCR was a strong predictor for DFS and overall survival and, in the CTneoBC analysis, patients

who achieved a pCR had a marked reduction in the risk of death (HR 0.36, 95% CI 0.31-0.42) compared to those with residual disease [23]. In this way, pCR may be used as an additional factor that adds significant information to the conventional prognostic factors. The prognostic effect of pCR has been reported to be stronger in triple-negative [12] and HER2-positive cancers [24]. In triple-negative tumors, patients with residual disease may have a worse prognosis, and may benefit from the addition of adjuvant capecitabine chemotherapy, as was shown in the Create-X trial [25]. Similarly, the Katherine trial showed that HER2-positive cancers that did not reach complete response after neoadjuvant trastuzumab-containing chemotherapy received substantial benefit with the substitution of trastuzumab-emtansine for trastuzumab in the adjuvant setting [26]. The results of these trials support the use of NAC in the vast majority of patients with HER2-positive or triple-negative breast cancer, since the outcome may positively influence subsequent patient management.

As the use of adjuvant chemotherapy in HR-positive, node-negative tumors is decreasing, in many breast centers chemotherapy prior to surgery has become the preferred use of chemotherapy in early breast cancer. The conversion of a clinically and/or pathologically node-positive axilla to pathologically node-negative could result in less radical surgery and a reduction in the incidence of lymphedema. pCR was not strongly related to DFS in this subset of patients; however, the prolonged course of highly efficacious postoperative endocrine therapy makes it more difficult to demonstrate an effect of pCR to survival outcomes. Similarly, residual disease is a weaker predictor for relapse in HR-positive and HER2-negative breast cancer patients, most likely highlighting the effect of adjuvant endocrine treatment.

Conclusions

This study highlights the importance of NAC in the treatment of early-stage breast cancer. We underline the efficacy and the feasibility of NAC in every-day clinical practice, as it may result in more conservative surgical interventions with fewer post-operative complications and guide the subsequent treatment, for the benefit of our patients. This study had some limitations, as it was a relatively small, retrospective analysis. However, real-world data are needed as patients treated in clinical practice will often be clinically distinct from patients included in randomized controlled trials (RCTs).

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Declarations of interest

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