ORIGINAL RESEARCH

Neoadjuvant chemotherapy among patients treated for nonmetastatic breast cancer in a population with a high HIV prevalence in Johannesburg, South Africa

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Background: Neoadjuvant (primary) chemotherapy (NACT) is the standard of care for locally advanced breast cancer. It also allows for the short-term assessment of chemotherapy response; a pathological complete responses correspond to improved long-term breast cancer outcomes. In sub-Saharan Africa, many patients are diagnosed with large nonresectable tumors. We examined NACT use in breast cancer patients who visited public hospitals in Johannesburg, South Africa.

Methods: We assessed demographic characteristics, tumor stage and grade, hormone receptor status, and human immunodeficiency virus (HIV) status of female patients diagnosed with nonmetastatic invasive carcinoma of the breast at Chris Hani Baragwanath Academic Hospital between January 1, 2009, and December 31, 2011. The patients received neoadjuvant, adjuvant, or no chemotherapy. Trastuzumab was unavailable. We developed logistic regression models to analyze the factors associated with NACT receipt in these patients.

Results: Of 554 women with nonmetastatic breast cancer, the median age at diagnosis was 52 years (range: 28–88 years). Only 5.8% of patients were diagnosed with stage I disease; 49.3% and 44.9% were diagnosed with stages II and III, respectively. Most patients had hormone-responsive tumors: luminal A, 38.1%; luminal B_1 (human epidermal growth factor receptor 2 [HER2]-negative and high grade), 12.5%, and luminal B_2 (HER2-positive any grade), 11.6%; 11.6% had a HER2-enriched tumor and 20.6% a triple-negative tumor. Eighty (14.4%) patients were HIV-positive. In total, 195 patients (35.2%) received NACT, 264 (47.7%) patients received adjuvant chemotherapy, and 95 patients (17.1%) received no chemotherapy, including 62 (11.2%) patients who received only hormonal therapy. Of patients receiving NACT, 125 (64.1%) were evaluable for clinical response. Eighty (64.0%) patients had a clinically significant response; 19 (15.2%) patients had a stable disease, and 26 (20.8%) patients had a progressive disease. Multivariate analysis showed age <40 years and disease stage to be independently associated with the receipt of NACT.

Conclusion: Most women receiving NACT with available response data showed a clinical benefit. Stage III disease at diagnosis and age <40 years were predictors of neoadjuvant versus adjuvant chemotherapy treatment.

Keywords: breast cancer, chemotherapy, neoadjuvant, South Africa, HIV, LMICs

Introduction

The incidence of breast cancer appears to be on the rise; 1.67 million new cases were diagnosed worldwide in 2012.[1,2] Low- and middle-income countries (LMICs) have lower incidence rates than high-income countries (HICs) but account for the majority

of breast cancer deaths.[3] Patients in sub-Saharan Africa (SSA) have poor breast cancer outcomes by the standards of HICs;[4] an estimated 50%–80% of breast cancers are locally advanced or metastatic at the time of diagnosis.[5,6]

Women with breast cancer in Africa have been reported to have earlier age at presentation and a higher proportion of more aggressive subtypes than women of European descent.[7] However, our Soweto, Johannesburg, and South African (SA) National Cancer Registry data revealed that, as in the USA, >60% of SA women present with the less aggressive, hormone-responsive luminal A and B breast cancer subtypes.[8,9] Furthermore, Surveillance, Epidemiology, and End Results (SEER) age-specific incidence rates of Black and White women are similar to those of the Johannesburg population (Figure 1).

Neoadjuvant (primary) chemotherapy (NACT) has become the standard of care for locally advanced breast cancer in HICs, particularly for more aggressive breast cancer subtypes such as human epidermal growth factor receptor 2 (HER2)-enriched breast cancer and triple-negative breast cancer (TNBC). NACT may facilitate breast-conserving surgery (BCS) by shrinking tumor size and decreasing nodal involvement, reduce the risk of adverse events after surgery, and provide early information about tumor response to chemotherapy.[10–16] An important end point of NACT is the induction of a pathological complete response (pCR) in resected tumors.[11,17] Because pCR has been associated with

an increase in disease-free survival (DFS) and overall survival (OS), it is often used as a surrogate for those end points in research clinical trials of NACT.[18–20]

New therapeutic agents are increasingly being tested prior to surgery in the hope that they will show higher rates of pCR than older agents.[21] Although many chemotherapeutic regimens have been used in the neoadjuvant setting, current guidelines recommend the use of an anthracycline-based regimen plus a taxane, along with HER2-targeted therapy when applicable and feasible.[22]

NACT is not well studied in breast cancer patients from LMICs, and the applicability or feasibility of applying HIC treatment guidelines to different patient populations is not known.[23,24] Studies in SSA have small sample sizes, lack uniform standards for treatment, and use differing chemotherapeutic regimens. Overall response to NACT in SSA, measured clinically rather than pathologically, varies from 30% to >90% in several reported studies.[25–28]

The Breast Health Global Initiative was convened to generate guidelines for breast cancer treatment in LMICs. The panel stratified care by the level of resource availability: basic, limited, enhanced, or maximal. The panel defined care at a basic level as what should be available in all health care systems, including the most under-resourced, and recommended anthracycline-based NACT as basic care for patients with locally advanced breast cancer. Treatment with taxanes and/or HER2-receptor inhibitors was recommended only for enhanced or maximal resource settings.[5]

Breast cancer care in much of SSA differs from the care provided to women in HICs because, in addition to resource constraints, LMICs have shortages of trained health care personnel, as well as cultural and educational barriers to care.[29,30]

Laboratory and radiotherapy equipment and their maintenance are also suboptimal. For example, a survey of 19 medical facilities in 14 different African countries found that only 7 locations had well-maintained radiotherapy capabilities and 8 had the means to perform immunohistochemistry.[31]

Without proper cancer screening or community education to promote breast cancer awareness, diagnoses are made later in the course of the disease, compared with HICs. Tumor sizes, at diagnosis, >10 cm accompanied by fungating breast masses are commonly reported.[25,26,32] In HICs, where breast cancer awareness is widespread and screening is readily available and widely promoted, breast tumors are usually smaller at diagnosis than those in LMICs.[33,34]

Observations that women in SSA have lower rates of luminal A and higher rates of TNBC have led some investigators to believe that breast cancers in SSA are inherently more
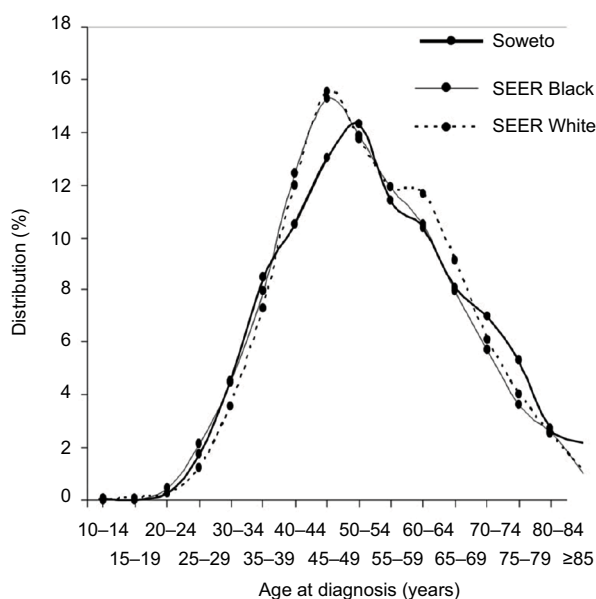

Figure 1 Age distribution of breast cancer incidence among women from Soweto, Johannesburg, and among US SEER Black and White women adjusted for Johannesburg population structure 2009–2011.
Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

aggressive than those in HICs due to unique environmental exposures or genetic mutations.[35] However, recent SA studies report breast cancer subtype distributions similar to those in the US populations.[8,9]

Compared with many of its neighbors, South Africa, an upper middle-income country, with an annual per capita gross domestic product (GDP) of ~US$7,000 and purchasing power parity GDP of ~$13,000,[36] has a relatively well-developed health care system, especially in the private sector. The public-sector health care service, which provides care to ~85% of the population, includes a number of relatively well-equipped and staffed tertiary/quaternary hospitals, although in more rural settings, patients face barriers to care similar to those confronting patients in low-income countries.[1,30,37]

To the best of our knowledge, no data have been published on the use of NACT among SA breast cancer patients. We have therefore analyzed the factors associated with the use of NACT among patients diagnosed at the Surgical Breast Unit at Chris Hani Baragwanath Academic Hospital (CHBAH) and then treated at the Medical Oncology Unit at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), both of which are large academic hospitals in Johannesburg.

Methods

CHBAH is a tertiary-care public hospital located in Soweto, in the southwestern part of Johannesburg, Gauteng Province, South Africa. It serves as the referral facility for 3–4 million people who live within 60 km of the hospital, as well as patients from farther afield.

The public health system in South Africa has a hierarchical referral system: primary care doctors and nurses refer patients with more complex conditions to secondary-level hospitals, which refer patients requiring still more complex evaluation and care to tertiary/quaternary facilities. CHBAH has a specialized Surgical Breast Unit where 15–25 new patients per month are diagnosed with breast cancer. Breast diagnoses, surgery, and follow-up are performed at CHBAH, while chemotherapy and radiation therapy are administered at CMJAH, 15 km from CHBAH.

Since 2006, the Surgical Breast Unit at CHBAH has maintained an electronic database of patient information. Since 2008, the Unit has been affiliated with the International Breast Centres Network and has standardized its treatment approach through weekly multidisciplinary meetings with cancer surgeons, medical oncologists, radiation oncologists, and palliative care specialists. In order to analyze the determinants of NACT, we reviewed the records of all female patients in the database diagnosed with Stages I–III invasive carcinoma of the breast from January 1, 2009, through December 31, 2011.

This study was approved by the University of the Witwatersrand Human Research Ethics Committee (Approval Number: M141129, dated December 5, 2014). The Committee did not ask us to obtain patients' consent because the study involved only retrospective medical record reviews. The data were anonymized for analysis to protect patients' confidentiality.

NACT

Most patients with Stages I and II breast cancer received primary surgery, while most patients with Stage III disease received NACT. The primary systemic regimens offered included 4 cycles of doxorubicin and cyclophosphamide followed by 4 cycles of paclitaxel (AC→T) or 6 cycles of 5-fluorouracil, doxorubicin, and cyclophosphamide. HER2-targeted therapy was not available for patients outside of a clinical trial. All patients with hormone-receptor-positive tumors received adjuvant tamoxifen. Patients with contraindications or intolerance of tamoxifen were offered anastrozole, an aromatase inhibitor, alone or, when applicable, in combination with goserelin, a long-acting gonadotropin-releasing hormone analog.

Data and statistical analysis

Data were abstracted from the electronic medical records in the CHBAH Surgical Breast Unit's database and the medical oncology records from CMJAH. The variables analyzed were patients' age, race, menopausal status, American Joint Committee on Cancer staging, histopathology diagnosis, tumor grade, estrogen receptor (ER)/progesterone receptor (PR) and HER2 status, as well as human immunodeficiency virus (HIV) status. Breast cancer subtypes were defined as luminal A (ER+ and/or PR+, HER2−, low/intermediate grade); luminal B_1 (ER+ and/or PR+, HER2 <3+, high grade); luminal B_2 (ER+ and/or PR+, HER2 3+, any grade); HER2-enriched (ER−, PR−, HER2 3+, any grade), and TNBC (ER−, PR−, HER2−, any grade). Ki67 analysis was not performed during the period of the study, although it is now available. Immunohistochemistry HER2–equivocal (2+) values were confirmed with in situ hybridization (ISH) results where they were available or defined as HER2− where ISH testing was not done.

We compared patients who received NACT to those who received adjuvant chemotherapy with respect to the variables listed above. Descriptive statistics such as frequencies and percentages were reported by means of tables for categorical

variables using the Pearson's χ^2 test and Fisher's exact test where appropriate (Table 1). Binary logistic regression was used to determine which factors were independently associated with NACT. All variables that were significant at $p<0.1$ on univariate analysis were evaluated in the multivariable model, and nonsignificant factors were dropped with stepwise backward regression. A two-sided p-value of <0.05 was considered significant throughout (Table 2). The analysis was

Table 1 Demographic and clinical characteristics of patients by chemotherapy category

Patient characteristics	Chemotherapy category								p-value
	Neoadjuvant		Adjuvant		No chemotherapy		Total		
	n	%	n	%	n	%	n	%	
	195	35.2	264	47.7	95	17.1	554	100	
Age group									<0.001
18–39	41	21.0	43	16.3	4	4.2	88	15.9	
40–49	48	24.6	70	26.5	5	5.3	123	22.2	
50–59	59	30.3	85	32.2	12	12.6	156	28.2	
60–69	29	14.9	47	17.8	15	15.8	91	16.4	
≥70	18	9.2	19	7.2	59	62.1	96	17.3	
Ethnicity									0.984
Black	179	91.8	241	91.3	86	90.5	506	91.3	
Asian	3	1.5	7	2.7	3	3.2	13	2.3	
Mixed/colored	6	3.1	8	3.0	3	3.2	17	3.1	
White	7	3.6	8	3.0	3	3.2	18	3.2	
Clinical stage at diagnosis									<0.001
IA-B	0	0	21	8.0	11	11.6	32	5.8	
IIA-B	17	8.7	204	77.3	52	54.7	273	49.3	
IIIA-C	178	91.3	39	14.8	32	33.7	249	44.9	
Tumor grade									<0.001
1	14	7.2	28	10.6	17	17.9	59	10.6	
2	85	43.6	115	43.6	48	50.5	248	44.8	
3	77	39.5	113	42.8	17	17.9	207	37.4	
Missing	19	9.7	8	3.0	13	13.7	40	7.2	
Histology on diagnosis									0.403
Invasive ductal carcinoma	181	92.8	251	95.1	88	92.6	520	93.9	
Invasive lobular carcinoma	6	3.1	9	3.4	6	6.3	21	3.8	
Mixed ductal/lobular carcinoma	2	1.0	2	0.8	0	0	4	0.7	
Others	4	2.1	1	0.4	0	0	5	0.9	
Missing	2	1.0	1	0.4	1	1.1	4	0.7	
Molecular subtype									<0.001
Luminal A	58	29.7	99	37.5	54	56.8	211	38.1	
Luminal B$_1$	23	11.8	38	14.4	8	8.4	69	12.5	
Luminal B$_2$	29	14.9	25	9.5	10	10.5	64	11.6	
HER2-enriched	20	10.3	37	14.0	7	7.4	64	11.6	
Triple-negative	51	26.2	54	20.5	9	9.5	114	20.6	
No data	14	7.2	11	4.2	7	7.4	32	5.8	
ER and PR expression									<0.001
ER+ alone	28	14.4	29	11.0	11	11.6	68	12.3	
ER+ and PR+	77	39.5	124	47.0	65	68.4	266	48.0	
PR+ alone	7	3.6	15	5.7	2	2.1	24	4.3	
ER− and PR−	83	42.6	96	36.4	17	17.9	196	35.4	
HER2 expression									0.744
HER2-positive	49	25.1	62	23.5	17	17.9	128	23.1	
HER2-negative	149	74.9	202	76.5	78	82.1	426	76.9	
Total	195	100	264	100	95	100	554	100	
HIV status on blood test									0.008
Negative	140	71.8	181	68.6	60	63.2	381	68.8	
Positive	31	15.9	41	15.5	8	8.4	80	14.4	
Unknown	24	12.3	42	15.9	27	28.4	93	16.8	

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HIV, human immunodeficiency virus; PR, progesterone receptor.

Table 2 Multivariable logistic regression model of predictors of neoadjuvant versus adjuvant chemotherapy

Predictors	OR	95% CI	P-value
HIV status			
Negative	1.00	Referent	
Positive	0.73	0.3–1.8	0.49
Unknown	1.06	0.4–2.6	0.90
Age group			
18–39	1.00	Referent	
40–49	0.32	0.1–0.9	0.02
50–69	0.37	0.2–0.9	0.03
≥70	0.18	0.05–0.7	0.01
Stage at diagnosis			
I & II	1.00	Referent	
IIIA-C	79.62	39.6–160.0	<0.001
Molecular subtypes			
Luminal A	1.00	Referent	
Luminal B$_1$	0.67	0.2–1.7	0.40
Luminal B$_2$	1.42	0.5–3.8	0.49
HER2-enriched	0.48	0.2–1.2	0.13
TNBC	1.50	0.7–3.4	0.32

Abbreviations: HER2, human epidermal growth factor receptor 2; HIV, human immunodeficiency virus; TNBC, triple negative breast cancer.

performed by using Stata Version 14 (StataCorp LP, College Station, TX, USA).

Results

Of the 554 women who met the criteria for inclusion in our analysis, 506 (91.3%) were Black and 211 (38.1%) were aged <50 years, including 88 (15.9%) women who were aged <40 years. At the time of diagnosis, 32 women (6%) were found to have Stage I, 273 (49.1%) Stage II, and 249 (44.9%) Stage III disease. In line with our previous reports for SA populations,[8,9] 211 (38.1%) patients had luminal A tumors; 69 (12.5%) had luminal B$_1$; 64 (11.6%) had luminal B$_2$, 114 (20.6%) had HER2-enriched tumors, and 114 (20.6%) had TNBC; and 32 (5.8%) had missing receptor subtype data. Overall, 426 (76.9%) patients had HER2− and 128 (23.1%) had HER2+ tumors. Fifty-nine (10.6%) patients had grade 1 tumors, 248 grade 2 (44.8%), and 207 grade 3 (37.4%) tumors, while 40 patients (7.2%) had missing data for tumor grade. Of 461 patients whose HIV status was known, 80 (17.4%) were HIV-positive (Table 1; 47 patients initially analyzed were found to have Stage IV disease and were excluded from the study).

Of the 459 patients (82.9%) who received chemotherapy, 195 (42.5%) received NACT, and 264 (57.5%) received adjuvant chemotherapy. Among women who received NACT, 178 (91.3%) had Stage III disease and 17 (8.7%) Stage II disease. No women with Stage I disease were treated with NACT. In contrast, among women treated with adjuvant chemotherapy,

21 (8%) had Stage I, 204 (77.3%) Stage II, and 39 (14.7%) Stage III disease.

Seven of the 195 (3.6%) women who received NACT subsequently had BCS, while 69 (26.1%) of the 264 women who had adjuvant chemotherapy had primary BCS. A further 15 women who had BCS were not referred for adjuvant chemotherapy.

Clinical response data were available for 125 (64.1%) patients who received NACT, of whom 80 (64.0%) patients were noted to have had a clinically significant response, 19 (15.2%) to have stable disease, and 26 (20.8%) to have the progression of their disease.

A multivariable logistic regression model controlling for age, HIV status, and tumor subtype found that women with Stage III breast cancers were >79 times as likely to receive NACT as women with Stage I or II breast cancer (Table 2).

Patients who tested positive for HIV and those with HER2-enriched tumors were less likely to receive NACT than uninfected patients and those with luminal A or B subtypes, but these differences were not statistically significant (Tables 1 and 2). Patients younger than 40 years were more likely to receive NACT than older patients, while race, tumor grade, and ER/PR status were not associated with the receipt of NACT (Table 2).

Discussion

In our sample of 554 women with nonmetastatic breast cancer, 17 of 273 (6.2%) women with Stage II and 178 of 249 (71.5%) women with Stage III disease received NACT. In our multivariable analysis, Stage III disease and age <40 years were the only independent predictors of receiving NACT (Table 2).

One of the purposes of NACT is to enable patients to receive more limited surgery than they would if the surgery preceded the chemotherapy. However, only seven of the 195 (3.6%) NACT recipients in our sample actually had BCS, although 80 of 125 (64%) of evaluable women receiving NACT had a clinically significant improvement, enabling mastectomy with clear surgical margins. As we have previously discussed, further study is needed to elucidate objective and pathological response rates and the extent to which NACT may facilitate BCS as opposed to mastectomy in our patient population.[38]

This study sheds light on the characteristics of female breast cancer treated in LMICs. About 35% of patients in this study received NACT, similar to that in HICs. Several large studies in the USA, including one of >250,000 patients, found that NACT was administered to 17%–36% of patients

with nonmetastatic breast cancer.[39–41] Similar to patients in our cohort, those in US samples were more likely to receive NACT if they had large tumors or late-stage disease. Most treatment guidelines call for NACT in patients with locally advanced breast cancer precisely because it can shrink inoperable tumors, facilitate definitive surgery, and increase the rates of breast conservation.[14,22,42–46]

Although not standard, preoperative chemotherapy may also be appropriate for patients with early-stage breast cancer. The National Comprehensive Cancer Network recommends NACT for operable tumors that have a high likelihood of responding to chemotherapy. NACT can provide predictive information on chemosensitivity, identify patients who may benefit from clinical trials of adjuvant therapies, and provide a setting to test novel medicines or biomarkers.[22]

In order for NACT to be predictive, the pathological response to chemotherapy must be ascertained. pCRs to NACT are strongly associated with improved DFS and OS among breast cancer patients.[18,47] Biologic agents, such as trastuzumab, have been highly effective in enhancing pCR when used in combination with NACT; >50% of patients achieve pCR in some studies.

Strengths and limitations

In our study, we did not have data on pathological response to NACT (given the limitations of retrospective studies of clinical record data), but 80 of 125 (64%) of the women achieved a clinically significant tumor response. This response rate is comparable to, although slightly lower than, those seen previously in HICs, as well as other SSA countries.[26,48,49] Future studies in this population should incorporate pathological response to NACT and determine whether NACT permits surgeons to perform more definitive surgery as well as BCS.

The proportion of women who tested positive for HIV in this study population (15.8%) was not higher than the prevalence of HIV among women of similar age in South Africa.[50] HIV has been implicated in the rise of some non-acquired immunodeficiency syndrome defining cancers, although not breast cancer.[51–53] Prior studies of SA women with breast cancer and HIV have not found an association between HIV and tumor characteristics, such as stage, grade, or molecular subtypes.[54] We did not find an association between NACT and HIV; HIV-positive patients (31 of 80 patients; 38.9%) were just as likely as HIV-negative patients (140 of 381 patients; 36.7%) to be referred for NACT (Table 2).

Findings among residents of Johannesburg may not be generalizable to more rural areas in South Africa or other countries in SSA. In addition, some data were missing regarding receptor status, lymphovascular invasion, HIV status, and pCR rates. Older women may have been underrepresented in our sample because of comorbid conditions and difficulties in accessing the health care system.[37]

The strengths of this study, however, include its relatively large sample size and the detailed data on tumor characteristics and breast cancer treatments.

Conclusion

NACT is the standard of care for women with locally advanced breast cancer in SA public hospitals. Most women who received NACT showed clinically significant benefit, although they generally did not receive biologic therapies such as trastuzumab. Only tumor stage and age <40 years were associated with the receipt of NACT. Future studies are needed to document the extent of clinical and pathological responses to NACT in South Africa, its acceptability to patients and their families, and its ability to improve breast cancer outcomes.

Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

Dr Ruff's institution received clinical research funding from Sanofi and Roche. Dr Neugut has served on the Medical Advisory Board of EHE, Intl. The other authors report no conflicts of interest in this work.

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