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ORIGINAL ARTICLE – BREAST ONCOLOGY

Axillary Pathologic Complete Response in Inflammatory Breast Cancer Patients: Implications for SLNB?

Folasade O. Imeokparia, MD[1], Tasha M. Hughes, MD[1], Lesly A. Dossett, MD, MPH[1], Jacqueline S. Jeruss, MD[1], Alfred E. Chang, MD[1], and Michael S. Sabel, MD[1]

Department of Surgery, The University of Michigan Rogel Cancer Center, Ann Arbor, MI

ABSTRACT

Background. Sentinel lymph node biopsy (SLNB) is increasingly utilized after neoadjuvant chemotherapy (NAC) in responsive adenopathy, particularly with placement of a marking clip in the involved node(s). This may allow a subset of patients to avoid axillary lymph node dissection. SLNB is still discouraged in inflammatory breast cancer (IBC). The purpose of this study is to examine the axillary pathologic complete response (AXpCR) in IBC patients with clinical adenopathy. There may be an implication to approach a subset of IBC patients for SLNB after NAC.

Methods. A single-institution institutional review board-approved database was reviewed. Inclusion criteria were clinicopathologic diagnosis of IBC and age $\geq$ 18 years. Stage IV disease was excluded. We collected data on demographics, tumor characteristics including histology and subtype, axillary status, and treatment effect details.

Results. Sixty-six patients fulfilled criteria. Mean follow-up was 4.1 years. The AXpCR was 6% for luminal A and luminal B [human epidermal growth factor receptor (HER)2 −] subtypes, and 24% for basal subtype. The AXpCR rate was 64% for HER2-enriched and luminal B (HER2 +) patients. Achievement of AXpCR among these HER2-positive patients was statistically significant (p = 0.0001). There was minimal difference in achieving AXpCR in HER2-overexpressing patients regardless of hormone receptor status (p = 1.000).

Conclusions. Understanding the best patients to select for use of SLNB or targeted lymph node dissection after treatment is evolving. This unique series identified and described the axillary pathologic characteristics of IBC patients following NAC. Further research is needed to confirm that the approach, axillary node clip placement prior to treatment, is feasible and accurate in IBC.

Guidelines on axillary lymph node management in invasive breast cancer have changed in a short period of time. In early-stage breast cancers, the role of sentinel lymph node biopsy (SLNB) and management of these nodes based on various pathologic results is well established.[1–3]

There is a growing body of work that details the pathologic results seen after neoadjuvant chemotherapy (NAC). NAC has improved long-term survival of patients with locally advanced disease, as well as pathologic response.[4–7] Despite the growth in understanding of how NAC varies in biologic response of disease, we are still trying to understand how to best utilize this information, for instance utilization as a surrogate endpoint.[8] Furthermore, use of SLNB after NAC is not as well established.

For inflammatory breast cancer (IBC), NAC became standard of care in the 1990s with MD Anderson publishing a detailed 20-year, single-institution experience.[9] Following this, our progression in understanding medical therapy for IBC grew substantially.[10–13] In 2008, the First International Conference on Inflammatory Breast Cancer assembled to establish "minimal guidelines" for the work-up and management of IBC. The panel declared "the only method of definitive surgery to be offered to women with IBC following preoperative systemic treatment is a modified radical mastectomy."[14] This "standard" has room for growth.

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F. O. Imeokparia, MD
e-mail: fimeokpa@med.umich.edu

The purpose of this study is to examine the complete axillary pathologic response (AXpCR) in IBC patients with clinically evident adenopathy and documented nodal disease. With the placement of a marking clip in involved node(s) prior to neoadjuvant chemotherapy (NAC), sentinel lymph node biopsy (SLNB) is increasingly being utilized after NAC. This approach is discouraged in inflammatory breast cancer (IBC) patients. It may be possible to approach a subset of IBC patients for SLNB following NAC, achieve adequate staging information, and avoid overutilization of axillary lymph node dissection (ALND).

METHODS

All patients with diagnosis of breast cancer treated by a multidisciplinary approach were entered into a prospective database approved by the institutional review board committee. The database spanned the time period from 2002 to 2018. For this study cohort, the larger database was filtered to identify the subset of patients who met the clinicopathologic diagnosis of IBC. Patients were $\geq$ 18 years old, with full documentation of completion of customary trimodal therapy for IBC: (1) neoadjuvant chemotherapy, (2) modified radical mastectomy (MRM), followed by (3) adjuvant radiotherapy. Patients with stage IV disease at diagnosis were excluded. Data were collected on demographics, preoperative axillary status, and tumor characteristics, including histologic receptor and subtype, as well as pathologic treatment effect details.

Patients were determined to have "clinically evident" adenopathy if physical examination and/or imaging suggested enlarged or abnormal-appearing lymph nodes. If patients had clinically evident adenopathy based on imaging alone, they went on to have confirmatory diagnosis of disease involvement with fine-needle aspiration (FNA), excisional biopsy, and/or core biopsy. Demographic, clinical, and postoperative pathologic details were analyzed among all patients identified with IBC. Statistical analysis was conducted using Fisher exact test for categorical variables. Multivariable analysis was not performed due to the small patient cohort number overall, and in each subtype. p values are two-sided and considered statistically significant when ≤ 0.05. GraphPad software was used to complete statistical work.

RESULTS

There were 66 patients who were analyzed for this study. All patients completed NAC plus trastuzumab $\pm$ pertuzumab when indicated, and underwent MRM and adjuvant radiotherapy. The median age of the cohort was 51 years.

Eight patients were of luminal A subtype (12%), nine were luminal B [HER2/neu negative] (14%), and ten were luminal B [HER2/neu positive] (15%). There were 18 patients who were of HER2/neu-positive enriched subtype, representing 28% of the cohort. Twenty-one patients were of basal subtype (32%). The demographics and clinicopathologic characteristics of the cohort are summarized in Table 1.

Of the 17 luminal A and luminal B (HER2/neu $-$) patients, sixteen (94%) had residual axillary disease following NAC. In other words, there was only a 6% AXpCR rate for those hormone-positive and HER2/neu-negative patients. For the 21 patients with basal subtype, the AXpCR rate was 24%, as residual disease was witnessed in 16 patients (Table 2).

The average number of positive lymph nodes after ALND was 10 for luminal A and luminal B (HER2/neu $-$) patients. For the basal subtype, the average number of positive lymph nodes was nine. The average number of positive lymph nodes found on ALND was only two for luminal B (HER2/neu $+$) and HER2/neu-enriched patients (Fig. 1).

The number of patients with AXpCR and the rate of this response subtype are summarized in Table 2 by subtype. There was a statistically significant difference in AXpCR among patients with any overexpression of HER2/neu ($p = 0.0001$) (Table 3). To further delineate the role of hormone receptor status in HER2/neu-overexpressing subtypes, luminal B (HER2/neu positive) and HER2/neu-enriched patients were compared. There was not a statistically significant difference in AXpCR by hormone receptor status ($p = 1.000$) (Table 4).

Mean follow-up for the cohort was 4.1 years. In this time period, we analyzed distant disease and overall survival (OS). HER2/neu-enriched and luminal B (HER2/neu-positive) patients had the lowest rate of distant disease at 21%. Luminal A and luminal B (HER2/neu-negative) patients had distant disease prevalence of 35%, and it was 67% for basal subtype. Overall, pathologic complete response (pCR), which included response in the breast and axilla, mirrored complete axillary pathologic response. HER2/neu-enriched subtype demonstrated 61% pCR. There were no luminal A and luminal B (HER2/neu-negative) patients who achieved pCR (Table 5).

TABLE 1 Demographics and clinicopathologic characteristics

Age, years [median (range)]	51 (23–82)
Ethnicity	
White	58 (83)
Black	5 (7)
Asian	1 (1)
Pacific Islander	1 (1)
Other	1 (1)
Tumor type	
Ductal	58 (88)
Lobular	2 (3)
Other	6 (9)
Subtype	
Luminal A	8 (12)
Luminal B (HER2–)	9 (14)
Luminal B (HER2 +)	10 (15)
HER2 enriched	18 (27)
Basal	21 (32)
Histologic grade	
I	1 (2)
II	20 (30)
III	39 (59)
NA	6 (9)
Number of axillary nodes removed	
1–15	25 (38)
16–30	33 (50)
30+	8 (12)
Number of positive axillary nodes removed	
0	24 (36)
1–3	7 (11)
4–9	18 (27)
10+	17 (26)
Surgery	
Unilateral mastectomy	36 (55)
Bilateral mastectomy	30 (45)
Systemic therapy	
ACT based	53 (80)
Other	13 (20)

Data expressed as *n* (%) unless otherwise specified

HER2 human epidermal growth factor receptor 2

NA not available, *ACT* adriamycin–cyclophosphamide–taxol

At time of data analysis, 57 patients were free of locoregional recurrence (LRR). Of these patients, 14 were of basal subtype, 17 were of HER2/neu-enriched subtype, and 7 were of luminal A subtype. Of the luminal B subtypes, i.e., both HER2/neu negative and HER2/neu positive, none of these patients were noted to have LRR.

TABLE 2 AXpCR by subtype

Subtype	AXpCR
Luminal A	1 (10)
Luminal B (HER2–)	0 (0)
Luminal B (HER2 +)	6 (60)
HER2 enriched	12 (67)
Basal	5 (24)

Data expressed as *n* (%)

AXpCR axillary pathologic complete response

HER2 human epidermal growth factor receptor 2

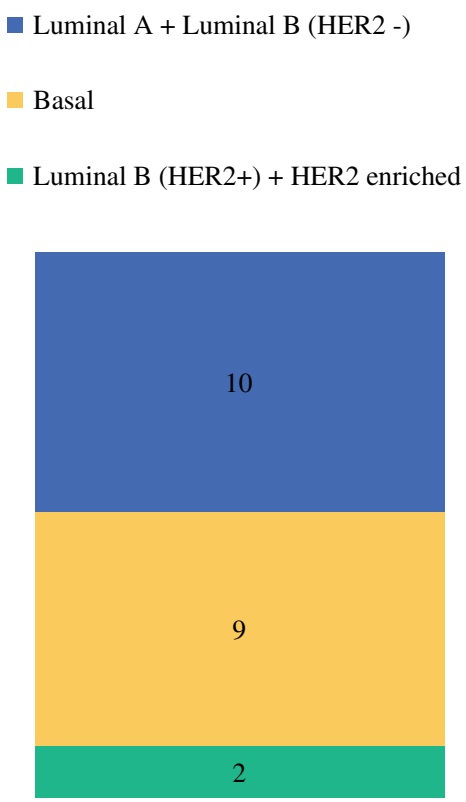

FIG. 1 Average number of positive LNs post-NAC

A total of nine patients had developed LRR at time of data analysis. One of these patients was of luminal A subtype with an occurrence of ipsilateral axillary adenopathy recurrence. An additional patient was of HER2/neu-enriched subtype with chest wall recurrence. The remaining seven patients with LRR were of basal subtype. Of these seven, four had chest wall LRR and three had supraclavicular lymph node adenopathy.

There were 24 patients in total who had AXpCR. These patients had different rates of LRR and distant recurrence (DR). The rate of LRR in patients with AXpCR was 4% (n = 1). The rate of DR was 21% (n = 5). The patient with

TABLE 3 AXpCR by HER2 disease status

HER 2 status	AXpCR	*p* value
HER2 positive [luminal B (HER2 +) + HER2 enriched]	18 (64)	0.0001
HER2 negative [luminal A + luminal B (HER2–) + basal]	6 (16)	

Data expressed as *n* (%)

HER2 human epidermal growth factor receptor 2

AXpCR axillary pathologic complete response

TABLE 4 AXpCR among HER2 + patients

Subtype	AXpCR	*p* value
Luminal B (HER2 +) [HR positive]	6 (60)	1.000
HER2 enriched [HR negative]	12 (67)	

Data expressed as *n* (%)

AXpCR axillary pathologic complete response

HER2 human epidermal growth factor receptor 2

HR hormone receptor

TABLE 5 Overall complete pathologic response by subtype

Subtype	pCR
Luminal A	0 (0)
Luminal B (HER2 −)	0 (0)
Luminal B (HER2 +)	3 (30)
HER2 enriched	11 (61)
Basal	3 (14)

Data expressed as *n* (%)

pCR overall pathologic complete response

HER2 human epidermal growth factor receptor 2

TABLE 6 Overall survival

Disease subtype	Overall survival
	Median (99% CI)
Luminal A + luminal B (HER2–)	3.14 (3.84–8.85)
Luminal B (HER2 +) + HER2 enriched	2.56 (2.34–5.64)
Basal	1.06 (0.55–4.21)

HER2 human epidermal growth factor receptor 2

CI confidence interval

AXpCR who developed LRR was of basal subtype. The majority (75%) of patients with AXpCR and no LRR were HER2/neu-enriched and luminal B (HER2/neu-positive) patients. The subtype of those with AXpCR who developed DR was basal in two patients and HER2/neu enriched in three patients.

Median OS for HER2/neu-enriched and luminal B (HER2/neu-positive) patients was 2.6 years. Median OS was 3.1 years for luminal A and luminal B (HER2/neu-negative) patients. Basal subtype patients had the lowest median OS of 1.1 years. Overall, 25 patients died of disease (36%) in the follow-up period. There were 57% alive without disease, and another 7% alive with disease. Luminal A, luminal B (HER2/neu negative), and basal subtype patients represented the majority of patients who had died of disease (Table 6).

DISCUSSION

Developments in breast surgery are more dynamic than ever. We increasingly appreciate the limitations of available treatment modalities, and we are seeking to apply existing interventions more judiciously. We have learned a great deal about innovative application of axillary management as per the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial, ACOSOG Z1071, and each year we learn more.

A brief review of SLNB in the realm of IBC is a prime example. In 2002, Stearns et al. conducted an evaluation of SLNB after NAC or neoadjuvant endocrine therapy in 34 patients with locally advanced breast cancer. While they were not the intended overall population, eight of the patients had IBC.[15] In 2009, Hidar et al. used a protocol for SLNB in 20 consecutive patients with IBC. In both studies, one tracer was used for SLN identification (blue dye), followed by SLNB, which itself was followed by ALND.[16]

These studies had variable success. Stearns et al. described identification of SLN in 75% of the IBC patients after NAC and Hidar et al. in 80%. The false-negative rate was 25% in the first study and 18% in the second. These studies inform us that the lymphatic pattern in IBC remains poorly understood. Both studies had important limitations including small cohorts, variable nodal status, and most notably that subtype could not be discerned.

In the current practice environment, placement of a marking clip in clinically evident node(s) prior to neoadjuvant chemotherapy has increased utilization of SLNB.[17–19] In the present study, we did not conduct identification of sentinel lymph nodes. We did find that

pathologic response mirrors non-IBC subtypes.[20,21] As evidence has mounted that SLNB after NAC is acceptable and feasible in patients who present with clinically evident, and/or pathologically confirmed metastatic lymph nodes,[18,22–24] it becomes important to make decisions on the best patients to select for this procedure. The use of SLNB in this way for patients with locally advanced disease has largely left out inflammatory breast cancer (IBC) patients.

Between 2013 and 2015, DeSnyder et al.[25] examined dual-tracer SLNB on 16 consecutive IBC patients. The SLN identification rate was 25% ($n = 4$). Two of the four patients who successfully mapped were HER2/neu enriched and two were basal. Out of these four patients, three had AXpCR. While it was not specifically discussed to which subtype the three patients with AXpCR belonged, they notably belonged to the subset of IBC patients in whom we found the highest rate of AXpCR in our evaluation (HER2/neu positive and basal).

This unique series identified and described the axillary pathologic characteristics of IBC patients following NAC. After analyzing our population of IBC patients, achieving AXpCR was statistically significant ($p = 0.0001$) among patients with HER2-positive disease. There was a modest impact of NAC on the basal subtype. We saw that almost two-thirds of HER2/neu-positive patients showed clinical response, which translated to a low axillary tumor burden and a low relative percentage of patients with development of distant disease. This analysis showed that this paradigm would be the least beneficial in patients with HR-positive subtypes.

ALND has significant physical morbidities and may have subsequent psychological sequelae as well. Whether ALND confers a survival benefit in IBC patients is a critical question. Several studies have tried to answer this, with variable conclusions.[26–28] SLNB after NAC could be selectively considered in a subset of IBC patients, possibly sparing these downstaged patients surgical morbidity from ALND. Further research is needed to confirm that the approach, axillary node clip placement prior to treatment, is feasible and accurate in IBC, and to better select patients who are unlikely to have complete pathologic response.

We acknowledge limitations of this study. The first is that this is a retrospective review of data, with the typical limits that have been recognized and detailed before. It would be best to describe and stratify results while limiting bias with a prospective trial randomizing arms of SLNB versus ALND in patients with IBC following NAC. Furthermore, for a particularly robust cohort, a multiinstitutional effort is ideal.

Additionally, we recognize that the role of the multidisciplinary team remains essential to the management of IBC patients. As the range of targeted agents available for breast cancer grows, these therapies will likely influence success of NAC. Further, radiation oncologists would be integral to discuss the function, if any, of regional radiotherapy on disease control.

Overall, we found an interesting narrative about the variable response to NAC in IBC patients. There was a considerable portion of HER2-overexpressing patients who may be acceptable candidates to be spared complete ALND. Perhaps, by using pretreatment clip placement or other localization measures for biopsy-proven axillary nodes, it may be feasible to obtain regional control of disease and maintain prognostic information, but eliminate ALND.

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