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BRIEF REPORT

Metaplastic breast cancer has a poor response to neoadjuvant systemic therapy

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Abstract

Objective Metaplastic breast cancer (MetaBC) is a rare breast cancer subtype poorly responsive to systemic therapy in the metastatic setting with high recurrence rates in the adjuvant setting. However, limited data exist regarding response to neoadjuvant chemotherapy (NAC). We performed a single institutional study to assess the clinical and pathological complete response rates (pCR) of MetaBC to NAC.

Methods Mayo Clinic Rochester patients with MetaBC treated with NAC were identified using the institutional medical index. Patient demographics, tumor characteristics, chemotherapy treatment, clinical and pathological response, and long-term outcomes were reviewed. Pathologic response was assessed by direct pathology review ($n=14$) or review of outside surgical and pathology reports ($n=4$).

Results Women with MetaBC ($n=18$) received NAC from January 1991 to June 2014. The mean age was 50 years (range 33–79) with a mean tumor size of 5.1 cm (range 2.3–11 cm) and 6/18 had pathologically confirmed lymph nodes prior to surgery. The majority (13/18; 72%) were estrogen receptor (ER), progesterone receptor (PR) and HER-2 negative (TNBC), and 1/18 (5.5%) was HER-2 positive. Five had BRCA testing and 2/5 were BRCA-2 positive. The chemotherapy regimens included anthracycline/cyclophosphamide (AC) ($n=1$), AC/taxane ($n=3$), AC/taxane/platinum ($n=8$), taxane/platinum-based regimens ($n=4$), taxane/cyclophosphamide ($n=1$) and taxane/trastuzumab ($n=1$). Five of 18 (28%) progressed on initial treatment including two who developed metastatic disease during NAC. The overall pCR rate was 2/18 (11%).

Conclusion MetaBC is poorly responsive to NAC, with a pCR rate (11%), that is lower than expected in a predominantly TNBC cohort. MetaBC patients should be considered for clinical trials testing new NAC regimens and in the absence of clinical trial enrollment, MetaBC patients with resectable disease should proceed directly to definitive operative management.

Keywords Metaplastic breast cancer · Neoadjuvant chemotherapy · Pathological and clinical outcomes

Abbreviations

AC(T)	Adriamycin/cyclophosphamide/(taxane)
BRCA-2	Breast cancer susceptibility gene-2

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EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
HER-2	Human epithelial growth factor-2
IDC	Invasive ductal carcinoma
KIT	Stem cell factor receptor
MetaBC	Metaplastic breast cancer
NAC	Neoadjuvant chemotherapy
pCR	Pathologic complete response
PR	Progesterone receptor
RCB	Residual Cancer Burden
TNBC	Triple-negative breast cancer
TP	Taxane/platinum
TC	Taxane/cyclophosphamide

Introduction

Metaplastic breast cancer (MetaBC) accounts for < 1% of all breast malignancies [1]. Metaplastic carcinomas represent a morphologically heterogenous group of invasive breast cancers in which a variable portion of the glandular epithelial cells comprising the tumor have undergone transformation into an alternate cell type, either a non-glandular epithelial cell type (e.g., squamous cell) or a mesenchymal cell type (e.g., chondroid, spindle cell, and osseous) [2, 3]. MetaBC is typically estrogen receptor, progesterone receptor and HER-2 negative (TN), high grade, with a propensity for recurrence. While single institution studies have demonstrated that MetaBC exhibits lower response rates [1, 4], the neo(adjuvant) systemic treatment for MetaBC is not well defined. Consequently, further data on the systemic management of MetaBC in this setting are needed.

The role of neoadjuvant chemotherapy (NAC) has expanded from its use in inflammatory and locally advanced tumors to patients with early stage breast cancer. The clinical utility of NAC in earlier stages of breast cancer has been best demonstrated in HER-2 positive and TNBC where pCR rates are substantial (30–50%) and associated with long-term survival [5]. In addition, patients with favorable response to NAC may be candidates for breast conserving surgery and sentinel lymph node biopsy, resulting in lower rates of axillary lymph node dissection [6–11].

We previously reported on characteristics, systemic therapies and clinical outcomes of 27 patients with MetaBC treated over a 20-year period [4]. Of eight patients treated with systemic therapy for metastatic disease, no patients achieved a complete response and a partial response was only experienced in one patient. Given these data and the paucity of data regarding the role of NAC for MetaBC, we performed a retrospective single institutional study to assess the clinical and pathological responses to NAC in MetaBC.

Methods

This study was approved by the Mayo Clinic Institutional Review Board. We queried the Mayo Clinic medical index (dates January 1991–June 2014) to identify patients with a diagnosis of MetaBC. The following terms were used for the search; "metaplastic breast cancer", "spindle cell cancer", "squamous cell cancer", "cancer with sarcomatoid features", "chondroid metaplasia", "bony or osseous metaplasia", "breast cancer-chondroid metaplasia", "breast cancer-sarcomatous metaplasia", "breast cancer-spindle cell metaplasia", or "breast cancer-squamous metaplasia". The medical records were then searched to confirm the diagnosis. Patients with stage IV disease, those who previously received adjuvant systemic chemotherapy for a prior breast cancer or who did not receive NAC were excluded. All diagnostic slides were available and were re-reviewed by two Breast Pathologists (DWV and MGK), to confirm the diagnosis of MetaBC.

Electronic medical records were used to review patient demographics, tumor characteristics, treatment received, and pathological response rates. Clinical tumor size was based on the largest size measurement identified on mammogram, ultrasound or MRI. Clinical lymph node status was determined by physical exam and imaging but not all clinically node positive patients had a confirmatory pre-chemotherapy needle biopsy. Recommendations for NAC were made on a case by case basis at the discretion of the treating breast care team including surgeon and medical oncologist. A pCR at surgery was defined as no evidence of invasive disease in the breast or axilla (ypT0 or ypTis, ypN0). Residual Cancer Burden (RCB) score after NAC was derived from the primary tumor bed area, overall cellularity, and percentage of cancer cells that were invasive or in situ disease, number of positive nodes and diameter of largest metastasis [12]. Post-treatment pathology slides were retrieved and re-reviewed for most patients ($n = 14$). Descriptive statistical analysis was utilized, and results are reported as frequencies (percentage) for discrete variables and as mean (SD) or median (range) as appropriate for continuous variables.

Results

A total of 18 female patients with MetaBC were treated with NAC over the study period and met the inclusion criteria. Patient and tumor characteristics are shown in Table 1. One patient had a previous history of TNBC in the contralateral breast treated with breast conservation surgery and radiation therapy without any adjuvant systemic

Table 1 Patient and tumor characteristics

Characteristic	
Mean age (range)	50 (33–79)
	N (%)
Clinical T category before NAC	
1	0 (0)
2	7 (39)
3	9 (50)
4	2 (11)
Clinical N category before NAC	
0	11 (61)[a]
1	3 (17)
2	2 (11)
3	2 (11)
Grade	
1	0 (0)
2	1 (5.5)
3	15 (83)
Not available	2 (11)[b]
Histologic features (biopsy)	
Matrix producing	5 (28)
Spindle cell	6 (33)
Squamous cell	4 (22)
Chondroid	2 (11)
Sarcomatoid	1 (5.5)
Type of breast surgery	
Breast conserving surgery	1 (5.5)
Mastectomy	16 (90)
None[c]	1 (5.5)
Type of axillary surgery	
Sentinel lymph node biopsy	7 (39)
Sentinel lymph node biopsy and axillary lymph node dissection	1 (5.5)
Axillary lymph node dissection	8 (44)
None	2 (11)

NAC neoadjuvant chemotherapy

[a]One patient developed nodal disease while on NAC

[b]Tumor size was too small to grade

[c]Patient progressed prior to surgical management

therapy. Five patients underwent genetic testing and 2/5 were BRCA2 positive. The mean tumor size was 5.1 cm (range 2.3–11 cm). One patient had multifocal disease. Eight patients presented with clinically node positive disease (six were histologically confirmed prior to surgery). The majority (13/18; 72%) were estrogen receptor (ER), progesterone receptor (PR) and HER-2 negative, and 1/18 (5.5%) was HER-2 positive. Pathology from core biopsies showed a diversity of histologic subtypes of MetaBC.

The individual chemotherapy regimens, clinical responses, RCB scores, and clinical outcomes are provided in Table 2. The chemotherapy regimens included AC/taxane (ACT) ($n=3$), ACT/platinum ($n=8$), taxane/platinum (TP) therapy ($n=4$), taxane/cyclophosphamide (TC $n=1$), and taxane/trastuzumab therapy ($n=1$). Seven patients either progressed ($n=5$) or had no radiographic response ($n=2$) to NAC. These seven patients were switched to an alternative chemotherapy regimen ($n=1$), proceeded to operative intervention ($n=4$), or switched to palliative management ($n=2$). For three patients, the clinical or radiographic status during NAC was unknown, although two of these patients developed recurrent disease after surgical management.

Table 2 Neoadjuvant chemotherapy with associated clinical responses and outcomes

ID	1st NAC	Number of cycles (total weeks)	Clinical response	2nd NAC (if any)	Number of cycles (total weeks)	Clinical response	Final surgery (RCB)	Local/distant relapse	Time to relapse (months)
Progression to metastatic disease									
1	TP	Two cycles (8 weeks due to delays for concern of abscess)	Initial clinical improvement, but radiographic progression and pulmonary metastatic disease on CT chest	None			N/A	Yes	0
2	AC (dd)	Four cycles (10 weeks due to delays)	Partial radiographic response on breast MRI	TP	Three cycles (11 weeks due to delays)	No response on CT chest	N/A	Yes	0
Clinical or radiographic progression on any NAC									
3[a]	T+Hsp90 inhibitor	1.5 cycles (5 weeks)	No radiographic response on breast MRI	TP	Three cycles (10 weeks due to delays)	Clinical and radiographic progression on breast MRI	III	Yes	1.5
4[b]	AC	Four cycles (12 weeks)	Partial radiographic response on CT chest	TP	Three cycles (9 weeks)	Clinical progression	III	Yes	8
5[c]	AC	Two cycles (6 weeks)	Clinical progression	None			II	Unknown	
No response or unknown response									
6[b]	TAC	Six cycles (18 weeks)	Unknown	None			Not available	Yes	4
7	AC (dd)	Four cycles (8 weeks)	Unknown	TP	Four cycles (8 weeks)	Unknown	Not available	Yes	11
8	AC +vincristine	Four cycles (8 weeks)	Partial response by breast MRI	TP	Four cycles (12 weeks)	Unknown	II	Yes	14
9	AC (dd)	Four cycles (9 weeks due to delays)	Unknown	T TP	One cycle (3 weeks) One cycle (3 weeks)	Unknown	II	None	–
10[a]	TP[4]	Four cycles (12 weeks)	Minimal radiographic improvement on breast ultrasound	None			II	Unknown	
11	TP	Four cycles (12–13 weeks due to delays)	Partial radiographic response on breast ultrasound	AC (dd)	Four cycles (8 weeks)	Unknown	II	None	–

Table 2 (continued)

ID	1st NAC	Number of cycles (total weeks)	Clinical response	2nd NAC (if any)	Number of cycles (total weeks)	Clinical response	Final surgery (RCB)	Local/distant relapse	Time to relapse (months)
12[e]	T	One cycle (3 weeks)	Radiographic progression on breast MRI	AC (dd)	Four cycles (8 weeks)	No response on MRI	II	None	–
	TP	Four cycles (12 weeks)	Clinical and radiographic improvement on breast MRI						
Radiographic or clinical improvement									
13	TC	Four cycles (12 weeks)	Radiographic improvement on breast MRI	None			II	Yes	10
14[f]	T + Herceptin	Four cycles (12 weeks)	Radiographic improvement	None			Not available	None	–
15	AC (dd)	Four cycles (8 weeks)	Clinical improvement	TP	Four cycles (8 weeks)	Clinical and radiographic improvement on PET-CT	Not available	Unknown	
16	AC (dd)	Four cycles (8 weeks)	Radiographic improvement on breast MRI	T (dd)	Four cycles (9 weeks due to delay)	Clinical improvement	I	None	–
Complete pathological response									
17[e]	AC (dd)	Four cycles (8 weeks)	Clinical and radiographic improvement on breast MRI	T (dd)	Four cycles (8 weeks)	Radiographic improvement on mammogram	0	None	–
18	TP	Four cycles (12 weeks)	Complete radiographic response on breast MRI	AC (dd)	Four cycles (8 weeks)	Complete response on breast MRI	0	None	–

A anthracycline-based therapy, *C* cyclophosphamide-based therapy, *T* Taxane-based therapy, *P* Platinum-based therapy, *dd* dose-dense

[a]Received adjuvant AC

[b]Received adjuvant hormonal therapy

[c]Received adjuvant TP

[d]Clinical trial J0785-Carboplatin/nab-paclitaxel/vorinostat

[e]Received adjuvant capecitabine

[f]Tumor is HER-2 + and patient received 1 year adjuvant Herceptin

Additionally, patients who experienced multiple delays and dose reductions due to toxicity were less likely to respond to NAC.

Of the 18 patients, surgical tissue was not available for review in 4/18 as surgery was performed elsewhere. In these four patients, surgical reports demonstrated residual disease. An additional two patients progressed to distant metastatic disease while on NAC. The majority of patients underwent a mastectomy ($n = 16$) and one underwent a lumpectomy. Sentinel lymph node biopsy was performed following NAC in 8 and 1/8 were positive necessitating an axillary lymph node dissection. One patient had a negative sentinel lymph node biopsy prior to NAC and 5/8 patients had histologically positive nodal disease after NAC.

Considering all 18 patients, two patients (11%) achieved a pCR. The two patients with pCR had TNBC (one with a BRCA-2 gene mutation) and received either ACT or ACT/platinum. The histologic subtypes of the two patients achieving a pCR were mixed metaplastic ductal/spindle cell carcinoma and metaplastic squamous cell carcinoma. In the remaining patients ($n = 13$) with final tumor size available, the mean residual tumor size was 5.8 cm (range 0.2–10 cm). Of the six patients with histologic confirmed nodal disease prior to surgery, two had a pCR in the axilla and four had residual nodal disease at surgery, including one who developed pathologically confirmed nodal disease while on NAC. Five patients received adjuvant systemic therapy following surgery (two anthracycline/cyclophosphamide, two tamoxifen, and one capecitabine).

At a median follow-up of 28.9 months (interquartile range 13.2–48.7 months), eight of 16 (50%) patients developed local ($n = 1$) or distant recurrences ($n = 7$) and six patients died of their disease. The median follow-up of the eight (50%) patients alive without disease at last follow-up was 42.2 months. One patient was lost to follow-up. Sites of disease recurrence included chest wall, bone, liver, lung, and brain.

Discussion

MetaBC is a rare breast cancer subtype, and this report is one of the largest single institutional studies evaluating the role of NAC for MetaBC. Five of 18 patients progressed during neoadjuvant therapy. Only four patients had some evidence for pathological response to treatment, including two patients with a pCR, one with a partial response in the breast, and two patients with axillary regional basins downstaged from node-positive to node-negative, one of whom achieved a pCR. Based on these findings, we would not recommend neoadjuvant systemic therapy with conventional regimens to patients with MetaBC presenting with surgically resectable disease outside of a clinical trial.

The treatment of MetaBC poses a dilemma to the treating physician because of poor response rates and high rates of disease progression, recurrence, and mortality [10]. Despite MetaBC patients frequently presenting with local–regionally advanced disease and being primarily a triple negative subtype, studies evaluating the efficacy of NAC in down-staging disease prior to surgery are limited [13, 14]. Our study builds on these data, demonstrating that MetaBC receiving NAC exhibit low tumor response rates and unacceptable rates of disease progression.

Studies to date have suggested that MetaBC is a distinct entity from other invasive ductal carcinomas. Molecular studies have shown that these tumors exhibit tend to be ER/PR/HER-2 negative, p63 and CK 5/6 positive, overexpress epidermal growth factor receptor (EGFR) and positive for stem cell factor receptor (KIT) [15–17]. Clinical studies have shown that MetaBC is likely to present as a rapidly growing mass, with a higher chance of fixation to skin or underlying musculature and is less likely to present with axillary lymph node metastasis [18]. This is consistent with findings in our study of a high rate of triple negative status, larger tumor size, and higher grade. Additionally, our finding that 2/5 patients who underwent genetic testing exhibited a deleterious BRCA2 mutation is consistent with the literature demonstrating a high rate of BRCA alterations in TNBC of around 10–30%, depending on ethnicity [19, 20].

Several studies comparing clinicopathological and prognostic outcomes of MetaBC and invasive ductal carcinomas reveal a worse prognosis for MetaBC with an increased risk of disease recurrence and poor overall survival [21–23]. A recent study by Nelson et al. using the Surveillance, Epidemiology and End Results database compared MetaBC to invasive ductal carcinoma (IDC) of the breast with the goal of identifying demographic, clinicopathologic, treatment, and survival differences [21]. The 5-year disease-specific survival was significantly worse for patients with MetaBC (78% vs. 93%, $p < 0.0001$). This worse prognosis persisted after controlling for hormone receptor negative status (77% vs. 85%, $p < 0.0001$). Song et al., investigating factors associated with poor prognosis, found larger tumor size (> 5.0 cm), lymph node involvement and a Ki-67 ≥ 14% were associated with a worse 5 year overall and disease-specific survival [22]. While studies have demonstrated a worse outcome comparing MetaBC tumors with non-MetaBC tumors [23], Leon-Ferre et al. using a large centrally reviewed cohort of over 600 TNBC treated at Mayo Clinic, demonstrated no differences in outcomes comparing MetaBC with other TNBC subtypes [24]. Our findings demonstrating a high rate of local and distant disease recurrence in 50% of patients and mortality in 1/3 with < 3 years of follow-up may simply be related to the high T and N stage of these patients.

A prior study from our institution evaluated the efficacy of systemic therapy in the adjuvant or metastatic setting

for metaplastic breast cancer for patients treated from 1976 and 1997 [10]. In this series, 26 patients presented with local-regional disease and 13 were treated with adjuvant systemic therapy with doxorubicin/cyclophosphamide, cyclophosphamide/methotrexate/5-fluorouracil, or cyclophosphamide/doxorubicin/5-fluorouracil. Disease-free survival and overall survival in these 26 patients were decreased compared with typical adenocarcinoma. Seven patients were treated in the metastatic setting with ten chemotherapy regimens with only one partial response (to doxorubicin).

A number of case reports and small series have showed similar disappointing results [25, 26]. A single institution study of 46 patients with MetaBC included 18 patients who were treated with systemic therapy in either the neoadjuvant ($n=12$) or palliative ($n=6$) settings [23]. Analyzed by regimen, no patient responded to anthracycline, vinorelbine, or cyclophosphamide. Three out of 17 patients who received taxane/platinum-based chemotherapy had a partial response. Of the patients that received NAC, the two with a response were treated with docetaxel/cisplatin and weekly paclitaxel/24 h high-dose infusional fluorouracil/leucovorin, respectively. Another study by Hennessy et al. demonstrated a pCR rate of 10% in a cohort of 21 patients receiving NAC for metaplastic sarcomatoid breast cancer [25]. Responders received four to six cycles of 5-flourouracil/doxorubicin/cyclophosphamide. Interestingly, a recent study by Ong et al. reviewed 2500 patients with MetaBC and found that chemotherapy use (19.4% NAC ± adjuvant, 57.4% adjuvant alone) versus no chemotherapy (24.9%) was significantly associated with improved survival, although the specific chemotherapy regimens utilized were not reported [27] and such a comparison most certainly has a selection bias. There was nodal downgrading in 20.7% of patients who received NAC, rates similar to our study. Patients included in our study represent a more contemporary cohort with evolution in the type of systemic therapy including the addition of taxane and platinum agents.

Although this study has some unique strengths including pathologic slide review to confirm the diagnosis and assess pathologic response (RCB) and the fact that many of the patients were treated in the modern era, our study does have some limitations. First, ours is a retrospective single institutional review that spanned over two decades, and no standard regimen of NAC was employed over this time period. Despite these limitations, this represents one of the larger single institution studies and serves to further support and confirm findings of prior smaller studies showing poor response of MetaBC to standard NAC. There is a clear need to identify specific targets and more effective regimens for this disease.

Conclusions

The management of patients with MetaBC remains a challenge due to the rarity of the disease, the small size of any single institutional experience and the poor responsiveness of these tumors to contemporary systemic therapy. This highlights the urgent need for new drug therapies for this tumor subtype. While there is no standard adjuvant therapy, the use of anthracycline and platinum-based therapies could be considered given higher pCR rates in unselected TNBC. However, based on our experience and the published literature, patients with MetaBC presenting with resectable disease should be either considered for clinical trial enrollment or proceed directly to definitive resection.

Author contributions ZAH and GC contributed equally to the data collection and interpretation, intellectual content and manuscript preparation. MGK and DWV reviewed pathology slides and assisted with manuscript preparation. JNI, MPG, and JWJ assisted with funding, intellectual content and manuscript preparation.

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Compliance with ethical standards

Conflicts of interest Matthew P. Goetz has consulting or advisory role: Eli Lilly, Novartis, Context Therapeutics, and Sermonix. Research Funding: Eli Lilly, Pfizer. Patents, Royalties, Other Intellectual Property: Methods and Materials for Assessing Chemotherapy Responsiveness and Treating Cancer; Methods and Materials for Using Butyrylcholinesterases to Treat Cancer. The other authors declare they have no competing interests and are in compliance with ethical standard.

Ethics approval This study was reviewed and approved by Mayo Clinic institutional review board committee under study ID: 14-008981.

Research involving human and animal participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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