Adjuvant Treatment of Triple-Negative Metaplastic Breast Cancer With Weekly Paclitaxel and Platinum Chemotherapy: Retrospective Case Review From a Single Institution

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Clinical Practice Points

- Metaplastic breast cancer (MBC) represents a cluster of rare malignancies. When the metaplastic histology is the predominant feature of the tumor, MBCs exhibit a basal-like gene expression profile and typically do not express receptors for estrogen, progesterone, or HER2 (triple negative, TN).
- Despite a low frequency of axillary nodal involvement, the prognosis of MBC is worse than that of TN ductal carcinomas. These tumors show a high rate of distant recurrence after patients are treated with conventional adjuvant cytotoxic regimens.
- Because of the recognized poor clinical outcome and given the lack of a standard of care for MBC, a clinical decision was made at our institution to offer patients whose tumors were TN and predominantly metaplastic an alternative to conventional anthracycline- and/or taxane-based adjuvant chemotherapy using a regimen of weekly carboplatin and paclitaxel.
- This case series summarizes the treatment and outcome of 23 patients with MBC who received adjuvant therapy at our institution over 15 years, 9 of whom were treated with a platinum/taxane combination therapy.
- At a median follow-up of 8.5 years for the series, all 9 patients treated with this combination were alive without evidence of disease.
- We discuss biologic factors that distinguish these tumors from other basal-like and TN breast cancers and provide a rationale for further basic and clinical exploration of this regimen for MBC patients.

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Introduction

Metaplastic breast cancer (MBC) is a rare histologic subtype that represents < 1% of all breast cancers and is defined by the differentiation of neoplastic epithelium into squamous and/or mesenchymal components.[1] The histology can be composed of squamous, fibromatosis-like, spindle-cell, or mesenchymal elements, which include chondroid and osseous differentiation. It is currently unclear what significance the various subtypes represent. MBC may be either entirely composed of metaplastic elements or a mixture of invasive ductal carcinoma (IDC) and metaplastic areas. As a result of this heterogeneity, the diagnosis of MBC is frequently missed on routine core biopsy analysis, and therefore accurate diagnosis is delayed until the time of tumor resection.[2]

Most cases of MBC are triple negative (TN) in that they do not express estrogen receptor, progesterone receptor, or HER2.[3-6] In contrast to other types of TN breast cancer (TNBC), it is unusual that these tumors involve regional lymph nodes. Metastatic spread to lung and bone is the most common pattern of dissemination.[7] Overall, MBC does not respond well to conventional chemotherapy, and despite the usual absence of nodal involvement, it has a

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worse prognosis compared to other TNBCs.[8-12] A study of Surveillance, Epidemiology, and End Results (SEER) data on patients with early and locally advanced MBC reported the 3-year overall survival of patients with TN MBC to be 75.4%. For stage I TN MBC, the 3-year overall survival was 91.4%, for stage II disease was 76.4%, and for stage III disease was 47.1%.[13]

In this report, we discuss the characteristics, treatment, and clinical outcomes of all patients who received adjuvant or neoadjuvant treatment for MBC over 15 years at our institution. The study was reviewed and approved by the local institutional review board.

Case Report

Pathology records between 2000 and 2015 identified 48 breast cancer reports that included the terms "metaplastic," "squamous," "spindle," "chondroid," or "osseous." Each of the cases was reviewed by an independent pathologist to confirm the diagnosis of MBC and to classify each tumor by subtype. Of the cases identified, 18 were reviews of pathology slides from other institutions. Five patients received adjuvant chemotherapy and follow-up at other institutions, and 2 were octogenarians who elected not to receive adjuvant chemotherapy. The remaining 23 patients are the subject of this review, including 3 patients who were initially diagnosed as having IDC but that was subsequently recognized as MBC. None had distant metastatic disease at presentation.

As a result of the lack of an established standard of care for adjuvant treatment of MBC, and because of poor outcomes reported with conventional adjuvant regimens, a clinical decision was made at our institution to offer patients whose tumor was TN and predominantly (> 50%) metaplastic an alternative platinum and taxane–based regimen that has known activity and toxicity in the treatment of breast cancer.[14-16] Although there is no standard for the extent of metaplastic change required to be classified as MBC, for treating outside of a clinical trial and for ethical reasons, the patients whose tumors were predominantly adenocarcinomas with lesser areas of metaplastic histology received standard-of-care treatment for IDC. Seven patients with predominantly TN MBC elected to receive the alternative regimen (carboplatin dosed at area under the curve = 2 plus paclitaxel 80 mg/m^2 weekly for 12 weeks) as their adjuvant treatment, and 2 other patients received a taxane/carboplatin combination, one after local recurrence and another who had a synchronous contralateral HER2-positive IDC. Of the 23 patients in this series, 9 were treated with a combination of platinum and taxane therapy; all 9 patients were alive and without evidence of disease at more than 5 years' follow-up (median, 8.58 years; range, 5.08-14.42 years). Of the 14 MBC patients treated with conventional adjuvant therapy, 6 died, and of these, 5 died of their disease.

The median age at diagnosis was 56 years (Table 1). Most patients were non-Hispanic white; 3 patients were Hispanic and 3 African American. Tumors were subtyped according to the World Health Organization classification.[1] Twelve tumors were identified as chondroid, 3 mesenchymal (not otherwise specified), 2 fibromatosis-like, 1 osseous, 1 spindle cell, 2 squamous cell, and 1 mixed squamous and chondroid histology. Median follow-up was 102 months (range, 29-177 months). All but 2 patients presented with high-grade malignancy. Fourteen patients had T2 and 4 had T3 tumors. Two patients in our series had involvement of axillary nodes associated with their MBCs, both of which were identified before neoadjuvant chemotherapy. Two additional patients had synchronous bilateral breast cancer; both had axillary nodal involvement on the side that did not have MBC. Only one of the tumors showing MBC exhibited expression of hormone receptors (HRs) in the nonmetaplastic portion of the tumor, and one exhibited HER2 amplification after neoadjuvant treatment that was not seen on diagnostic biopsy. All other metaplastic tumors showed no expression of HRs or HER2. Patients were treated with surgery and radiation according to standard treatment guidelines.

Patients 4, 9, 12, 14, 16, and 17 were treated with adjuvant carboplatin and paclitaxel and have remained free of disease since their initial treatment. Of note, patient 9 had a reaction to carboplatin after week 7 and completed the regimen with cisplatin at 75 mg/m^2 every 3 weeks for 2 doses along with continued weekly paclitaxel. Patient 3 had a 3.1 cm moderately differentiated tumor showing fibromatosis-like histology and received a weekly carboplatin/paclitaxel adjuvant regimen. She experienced an isolated pulmonary recurrence 6 years later when she underwent imaging for evaluation of chest pain. She was treated by wedge resection, and pathology confirmed recurrence of MBC. She did not receive further systemic therapy and remains in remission after 8 years of additional follow-up.

One patient (patient 8) was initially diagnosed with MBC by core biopsy and was enrolled onto a neoadjuvant clinical trial, on which she received docetaxel and capecitabine followed by doxorubicin and cyclophosphamide. She subsequently underwent a lumpectomy and sentinel lymph node biopsy followed by local radiation. Pathology revealed a single microscopic focus (< 1 mm) of residual disease in the breast. Four years later, she developed an ipsilateral breast recurrence showing MBC and had a completion mastectomy with reconstruction. She was then treated with weekly carboplatin and paclitaxel for 12 weeks, and she exhibited no further disease recurrence in more than 5 years' additional follow-up.

Patient 19 was diagnosed with 2 independent primary breast cancers—on the left a 5.3 cm MBC with no nodal involvement and on the right a multifocal, HER2-positive cancer involving 1 of 9 axillary nodes. After bilateral mastectomy, she received adjuvant therapy with docetaxel, carboplatin, and trastuzumab as standard therapy for HER2-positive disease, thus providing platinum and taxane chemotherapy for her MBC as well. She has been free of disease for more than 5 years.

Of the remaining 14 patients in this series, 8 received adjuvant treatment with doxorubicin and cyclophosphamide or docetaxel and cyclophosphamide, 2 of whom had T1 tumors. Four patients received doxorubicin and cyclophosphamide followed by paclitaxel, 3 of whom were treated before surgery. An additional patient (patient 6) had a 1.5 cm grade 1 tumor and received no systemic treatment. She experienced a local recurrence treated with surgery and radiation only, and has remained in remission after 6 additional years' follow-up. One other patient (patient 7) had a 1.4 cm HR-positive ductal carcinoma with 25% of the tumor showing HR-negative squamous carcinoma. She received adjuvant therapy with tamoxifen and died without evidence of recurrent cancer. Eight of these 14 patients survive, all without evidence of disease.

Table 1 Clinicopathologic Characteristics

Patient No.	Age at Diagnosis (Years)		Classification	Grade	Size of Primary Lesion (cm)	Adjuvant Chemotherapy	Recurrence	Follow-up (Months)	Current Status
1	52	W	Chondroid	3	9	AC	Lung, bone, brain at 7 months	12	Deceased
2	31	AA	Chondroid	3	4.9	AC	No	182	NED
3	60	W	Fibromatosis	2	3.1	C/T	Lung at 6 years	168	NED
4	64	W	Mesenchymal NOS	3	5	C/T	No	173	NED
5	57	W	Chondroid	3	9	AC	Bone at 26 months	27	Deceased
6	68	W	Fibromatosis	1	1.5	None	Local at 2 years	102	NED
7	64	W	Squamous[a]	3	1.4	None	No	41	Deceased
8	47	W	Chondroid	3	3.5	XT-AC (neo); C/T	Local at 4 years	117	NED
9	69	H	Osseous	3	2.5	C/T	No	120	NED
10	56	AA	Chondroid	3	3	AC	No	111	NED
11	50	W	Chondroid	3	5.5	AC-T	No	113	NED
12	40	H	Mesenchymal NOS	3	2.3	C/T	No	103	NED
13	67	W	Spindle cell	3	1.2	AC	No	100	NED
14	44	W	Mesenchymal NOS	3	3	C/T	No	85	NED
15	34	H	Chondroid	3	2.5	TC	No	86	NED
16	61	W	Chondroid	3	1.1	C/T	No	88	NED
17	56	W	Chondroid	3	2.3	C/T	No	91	NED
18	64	W	Chondroid	3	0.7	TC	No	69	NED
19	46	W	Chondroid	3	5.3	TCH	No	61	NED
20	68	W	Squamous	3	3.1	TC	No	70	NED
21	57	W	Squamous + chondroid	2	4.1	AC-T (neo)	Lung at 6 months	10	Deceased
22	51	W	Metaplastic NOS	3	3.3	AC-T (neo)	Brain at 19 months	23	Deceased
23	40	AA	Chondroid[b]	3	3	AC-T (neo)	Lung, bone, brain at 15 months	23	Deceased

Abbreviations: AA = African American; AC = doxorubicin and cyclophosphamide; AC-T = doxorubicin and cyclophosphamide followed by paclitaxel; C/T = carboplatin and paclitaxel; H = Hispanic; NED = no evidence of disease; neo = neoadjuvant chemotherapy; NOS = not otherwise specified; TC = docetaxel and cyclophosphamide; TCH = docetaxel, carboplatin, and trastuzumab; W = white; XT = capecitabine and docetaxel.
[a]Nonmetaplastic portion of tumor was estrogen receptor positive.
[b]Postneoadjuvant treatment tumor was HER2 positive.

Discussion

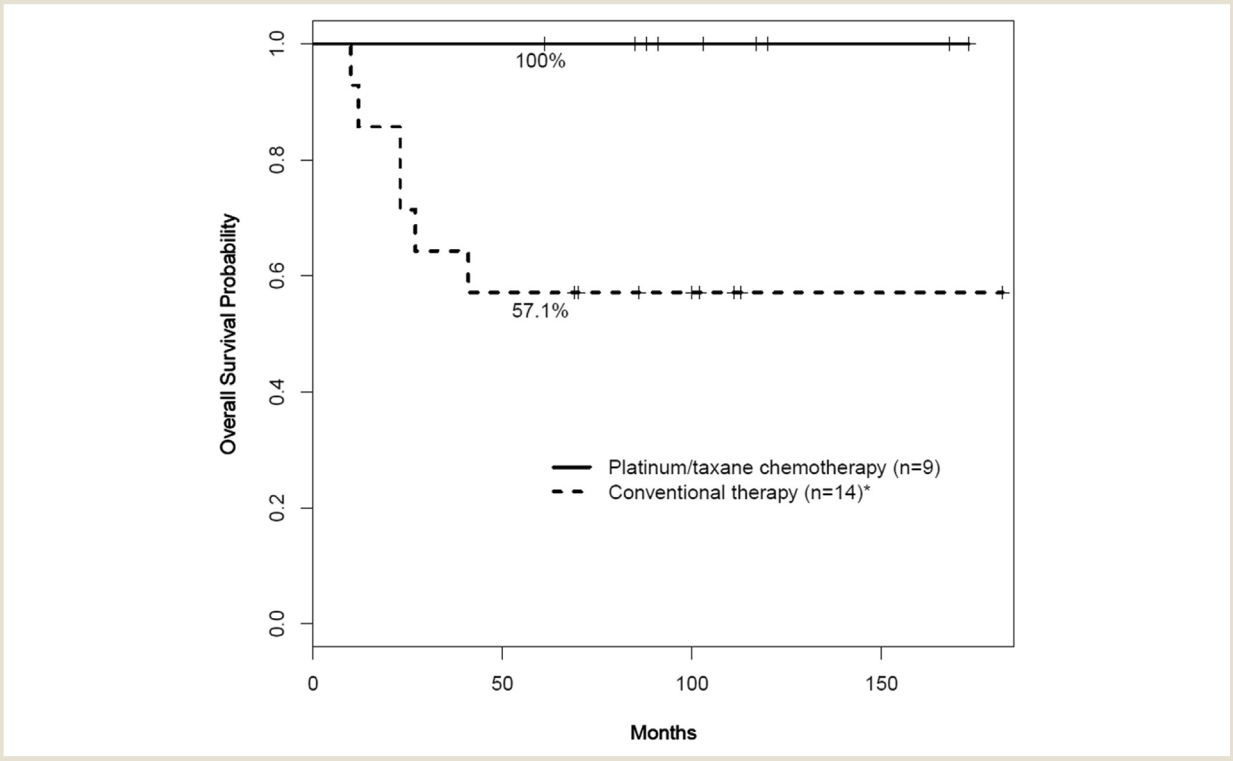
All surviving patients continue follow-up in our breast cancer survivors' clinic. No patient experienced unexpected adverse effects from chemotherapy. Of the 8 patients who were treated with weekly carboplatin and paclitaxel, 2 experienced significant neutropenia and continued treatment on schedule with the support of weekly doses of filgrastim. As mentioned above, one patient had a reaction to carboplatin on week 7, and her treatment was completed using cisplatin.

Figure 1 provides a Kaplan-Meier plot of overall survival for our patients treated with platinum/taxane adjuvant therapy and that of our patients treated with conventional adjuvant therapy. Because this is a retrospective case series, patients were not randomly assigned to platinum-based or conventional therapy, and the stage distribution is different in the 2 cohorts. In light of these considerations, a formal statistical comparison of the 2 cohorts is not appropriate. Instead, we chose to calculate the probability that the 9 platinum/taxane-treated patients would have survived irrespective of treatment modality. We noted that 7 of the 9 patients in our series treated with platinum/taxane therapy had T2N0 TN disease at diagnosis; 1 had T3N0 disease and 1 T1N0. Accordingly, we queried the national SEER registry to determine the expected 5-year survival probability of patients with T2N0M0 TN MBC. We used the SEER*Stat software and the International Classification of Diseases for Oncology, version 3 (OCD-O-3), morphology codes 8052, 8070, 8071, 8072, 8074, 8560, 8571, 8572, 8575, and 8980 to identify T2N0M0 TN female malignant MBC cases for the years 2010 through 2014, including 18 SEER registry data sets.[13,17] Cases without follow-up information were excluded from the analysis. Using the Kaplan-Meier method, we determined that the expected 5-year survival for T2N0M0 TN MBC is 75%. Because of the small number of patients in this platinum/taxane cohort, and assuming an expected 5-year survival of approximately 75% based on SEER data, using a simple binomial probability calculation, the likelihood that all 9 of our patients treated with platinum/taxane therapy would survive more than 5 years is $(0.75)^9 = 7.5\%$, which is unlikely to have occurred by chance.

Of the 14 patients in our series treated with conventional therapy, 8 remain alive and currently have no evidence of disease. The clinical outcome of these patients treated with conventional adjuvant therapy is similar to that reported by other investigators. In a recently reported single-institution study of MBCs diagnosed over a 10-year period in which tumor pathology was carefully reviewed, although 72% of patients had T1 or T2 lesions, 44% of the patients died of their disease.[18] Another single-institution study with thorough pathology review showed a 5-year distant recurrence rate of 35%.[2] In contrast, all 9 of our patients who received a platinum/taxane doublet as adjuvant therapy are currently without evidence of cancer, all with more than 5 years' follow-up.

Our patients' clinical outcome suggests that their tumors were sensitive to platinum-based chemotherapy. In this regard, an intriguing feature of MBC is the high degree of *BRCA* dysfunction

Figure 1 **Overall Survival for Metaplastic Breast Cancer. Overall Survival Is Shown for Patients Treated With Conventional Adjuvant Therapy or Platinum/Taxane Chemotherapy. Two Patients Treated With Conventional Therapy Did Not Receive Chemotherapy. *One Patient Who Received Conventional Therapy Died Without Cancer Recurrence**



found in these tumors. One study showed that 63% of MBCs exhibit methylation-induced *BRCA1* silencing, compared to 12% of control specimens.[19] *BRCA1* dysfunction, including gene silencing, has been proposed as a feature of tumors with potential sensitivity to platinum-based chemotherapy.[20] A study using *BRCA*-deficient TNBC patient-derived xenographs showed that *BRCA1* promoter methylation that resulted in loss of *BRCA1* expression in tumors yielded sensitivity to platinum agents and poly(ADP-ribose) polymerase inhibitors similar to *BRCA1*-mutant tumors. They further demonstrated that in patients receiving neoadjuvant chemotherapy, residual (therapy resistant) disease resected at the time of definitive surgery displayed reduced *BRCA1* methylation and increased *BRCA1* messenger RNA levels compared to their prechemotherapy control values.[21] Thus, the degree of *BRCA* dysfunction found in untreated MBCs, and hence responsiveness to platinum-based therapies, may be significantly greater in tumors without prior exposure to conventional chemotherapy. These observations suggest that in a disease such as MBC, the ideal setting to test the efficacy of platinum-based therapy may be in patients without prior exposure to other conventional cytotoxic agents. This was the case with all but one of the platinum-treated patients in our series.

New possibilities are continually emerging for the treatment of breast cancer. Although a proportion of MBCs has been shown to express potential therapeutic targets such as *PIK3CA* mutations and expression of programmed death ligand 1, it is important to recognize that MBCs differ in fundamental and significant ways from other TNBCs.[22-24] For example, although most MBCs exhibit a basal-like genomic profile, a distinctive biologic feature shown by transcriptome analysis is that compared with basal-like IDC, MBCs exhibit significant down-regulation of PTEN and TOP2A, which may contribute to a degree of chemoresistance to anthracycline-based therapies.[25] Other studies have shown that MBCs are frequently enriched in markers of epithelial-to-mesenchymal transition and stem cell–like features that distinguish them from other basal-like or luminal cancers.[26,27] Consistent with these findings, a high percentage of MBCs express the p53 homolog nuclear transcription factor p63, which is necessary for mammary development but which is only rarely expressed in IDCs.[28,29] In summary, although MBCs represent a heterogeneous cluster of rare breast tumors, they are also distinct in several ways from IDCs, and specifically from TN IDCs. These distinctive features of MBC suggest that results of clinical studies involving broader populations of patients with TNBC may not be applicable to this subgroup and may require independent validation for patients whose tumors have metaplastic histology. Moreover, whether patients' tumors express specific targets or not, an optimal chemotherapy backbone remains important and the results of our limited case series suggest that for adjuvant therapy of MBC, initiation of treatment with a platinum/taxane doublet may be valuable.

Patients with TNBC whose tumors show a pathologic complete response after neoadjuvant chemotherapy have improved overall survival compared to those who have residual disease at surgery.[30] As a result, there has been interest in clinical trials that improve pathologic complete response. Two such studies, Cancer and Leukemia Group B (CALGB) 40603 and the German Gepar-Sixto, have shown that the addition of carboplatin to anthracycline and taxane chemotherapy improved the pathologic complete response rate in both studies by approximately 15%.[31,32] Although not powered to assess overall survival benefit, these trials have resulted in an increased use of carboplatin in the neoadjuvant setting for TNBC to maximize the number of patients in a good-prognosis group. In both trials, carboplatin was incorporated in the treatment regimen starting with the first cycle of chemotherapy. Consistent with the results of our patients' experience, a chemotherapy regimen such as that used in CALGB 40603 of carboplatin plus weekly paclitaxel followed by dose-dense doxorubicin/cyclophosphamide may be appropriate for treatment of MBC. Our patients with TN node-negative MBC, however, received a platinum/taxane doublet in the adjuvant setting but without anthracycline chemotherapy. This raises the question of to what degree the addition of anthracycline treatment can improve clinical outcome in this rare and biologically unique subset of TNBC. Such a question is appropriate to address in a multi-institutional effort to optimize treatment with minimal toxicity for these patients.

Our small series cannot provide a definitive recommendation about routine clinical management. However, for adjuvant treatment of metaplastic node-negative breast cancer, if patients receive initial therapy with carboplatin and paclitaxel, we believe the subsequent addition of anthracycline chemotherapy should be at the discretion of the treating physician after a thorough discussion with the patient taking into account the patient's performance status and wishes as well as potential anthracycline toxicities.

Conclusion

Pure MBC is a rare subtype of breast cancer that is often high grade, HR negative, and poorly responsive to conventional chemotherapy. We describe the treatment and outcomes of 23 patients treated over 15 years at a single institution. The 14 patients who received conventional adjuvant therapy experienced similar outcome to patients reported by other institutions. In contrast, of the 9 patients treated with a platinum/taxane combination, which was well tolerated, all are alive, and only one has experienced a distant recurrence, which was successfully treated by metastectomy. Data from SEER indicate that the expected 5-year survival for T2N0M0 TN MBC, irrespective of treatment, is 75%. Using this estimate, we calculated the probability that all 9 patients in our series treated with a platinum/taxane doublet would survive more than 5 years is just 7.5%, thus suggesting the platinum/taxane regimen is likely effective and responsible for the improved survival of these patients.

To our knowledge, a regimen of weekly paclitaxel and carboplatin has not been reported for adjuvant treatment of MBC. A limitation of our study is that because our patients were treated before the recommendation to expand germ-line testing for *BRCA* mutations to all TNBC patients up to age 60 years, data on germline mutation status of these patients are incomplete at this time. Also, similar to other reports in MBC, we acknowledge the limitations of the small size of this series.

Despite these considerations, the results from our small study suggest that the role of a low-dose weekly platinum/taxane doublet as initial therapy for adjuvant treatment of MBC deserves further clinical and laboratory investigation.

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Disclosure

The authors have stated that they have no conflict of interest.

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