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ORIGINAL RESEARCH

Promising Response to Neoadjuvant Chemotherapy Plus Immunotherapy in Metaplastic Breast Carcinoma

Qingjian Tan*, Na Li*, Yan Wang, Tian Du, Gehao Liang, Zixuan Zhao, Jun Tang, Hao Wu

Department of Breast Cancer, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-Sen University Cancer Center, Guangzhou, Guangdong Province, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jun Tang; Hao Wu, Email tangjun@sysucc.org.cn; wuhao1@sysucc.org.cn

Purpose: Metaplastic breast carcinoma (MpBC) is a rare and aggressive subtype of breast cancer that often shows poor response to conventional neoadjuvant chemotherapy (NAC). This study aimed to evaluate the efficacy of combining NAC with immune checkpoint inhibitors (ICIs) in MpBC patients.

Methods: We conducted a retrospective analysis of MpBC patients treated with NAC, with or without the addition of immunotherapy, at Sun Yat-sen university Cancer center between 2017 and 2024. We assessed clinical and pathological response to NAC in MpBC patients.

Results: 40 MpBC patients treated with NAC were identified, 33 patients treated with NAC alone, 7 patients treated with NAC and immunotherapy, 4 (10%) patients achieved pCR. Among the 33 patients treated with NAC alone, only 2 (6%) achieved pCR. In contrast, 7 patients received additional immunotherapy, and 3 started immunotherapy at the initiation of NAC, with 2 of these (67%) achieving pCR. Patients who received immunotherapy after disease progression on NAC showed varying degrees of tumor response, from stable disease (SD) to partial response (PR).

Conclusion: We observed a promising response on addition of immunotherapy to NAC among patients with MpBC, suggesting that immunotherapy may have great potential in the treatment of metaplastic breast carcinoma.

Keywords: metaplastic breast carcinoma, neoadjuvant chemotherapy, pathological complete response, immunotherapy

Introduction

Metaplastic breast carcinoma (MpBC) is a rare and aggressive subtype of breast cancer, accounting for less than 1% of all invasive breast malignancies.[1–3] It comprises various histological subtypes, including squamous cell carcinoma, sarcomatoid carcinoma, and chondroid carcinoma, and predominantly affects relatively younger patients. Most MpBC cases are classified as triple-negative breast cancer (TNBC), which is associated with poorer clinical outcomes.[4] Ong et al reported that the 5-year overall survival rate for stage I–III MpBC patients is 72.5%, significantly lower than the 87.5% seen in non-MpBC breast cancers ($p < 0.001$).[2] Another retrospective analysis from the US National Cancer Database indicated a 5-year overall survival rate of 63.1% for MpBC patients, further emphasizing the lower survival rates compared to other breast cancer subtypes.[5]

While neoadjuvant chemotherapy (NAC) is the standard approach for high-risk early-stage TNBC, MpBC has shown a significantly lower response to conventional NAC.[6–15] Studies have demonstrated that the pathological complete response (pCR) rate for MpBC remains low, typically between 10–15%,[8,9,11–15] which is considerably lower than that of other breast cancer subtypes. This limited response to NAC highlights the need for alternative therapeutic strategies to improve outcomes in MpBC patients.

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Immune checkpoint inhibitors, particularly PD-1/PD-L1 inhibitors, have demonstrated efficacy in several highly immunogenic cancers, including non-small cell lung cancer, melanoma, and TNBC.[16–18] Given MpBC's poor response to standard chemotherapy and its immunogenic potential, there is growing interest in exploring the role of immunotherapy in this subtype.

The objective of this study is to evaluate the impact of combining NAC with immune checkpoint inhibitors in MpBC patients, with a focus on improving pCR rates and treatment outcomes.

Materials and Methods

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Sun Yat-sen University Cancer Center. The permit number was B2024-672-01. Given that our research is a retrospective study utilizing a subset of patient medical records, it meets the following criteria: the risk to participants is minimal, and patient confidentiality will be fully protected. The inclusion of the relevant patient population is rare, and obtaining informed consent in this context would not be practical. Furthermore, previous studies had already obtained written consent from participants for the use of their medical records in additional research endeavors. In compliance with ethical guidelines, we submitted a request to the Ethics Committee of Sun Yat-sen University Cancer Center for a waiver of informed consent, which was subsequently approved.

Patient Cohort

Eligible participants in the study had a definitive diagnosis of MpBC, confirmed through pathological examination of either postsurgical specimens or core biopsy samples, with no evidence of distant metastasis. All participants received chemotherapy before surgery. There were no restrictions on sex or age for patient eligibility in this study. From 2017 to 2024, we identified 51 patients with MpBC who received NAC followed by surgery in our institutional database. Eleven patients were excluded from the analysis; a summary of the patient screening process is shown in Figure 1. Finally, a total of 40 patients were deemed eligible for inclusion in the study. Data were extracted from the patients' medical charts,

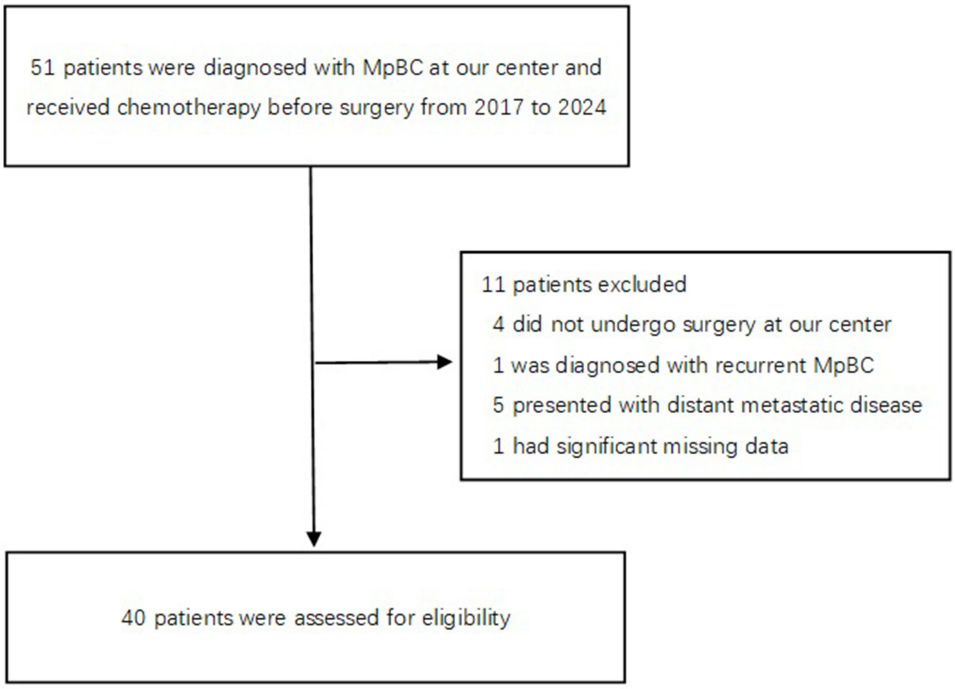

Figure 1 Patient eligibility flowchart. This flowchart outlines the patient selection process for the study. A total of 51 patients were diagnosed with metaplastic breast carcinoma (MpBC) at our center and received chemotherapy prior to surgery between 2017 and 2024. Eleven patients were excluded for the following reasons: four did not undergo surgery at our center, one was diagnosed with recurrent MpBC, five presented with distant metastatic disease, and one had significant missing data. Forty patients were assessed for eligibility.

including age at diagnosis, tumor stage (tumor size and local lymph node involvement), presence of ductal carcinoma components, Ki-67 proliferative index, hormonal receptor status, HER2 status, and types of systemic treatment, radiotherapy, and surgery.

Pathologic Evaluation

Clinical response was assessed through both clinical examination and radiologic evaluation using RECIST criteria.[19] Pathologic complete response (pCR) is defined as the absence of invasive components in both the primary tumor and lymph nodes, regardless of any residual ductal carcinoma in situ (ypT0/pTis ypN0). Assessment of estrogen receptor, progesterone receptor, and HER2 status was conducted according to ASCO/CAP guidelines.[20,21]

Result

Clinicopathological Characteristics

The clinicopathologic characteristics of patients prior to NAC, along with their treatment plans, are summarized in Table 1. Among the 40 female patients, the median age at diagnosis was 44 years (range: 27–70 years), and the median tumor size was 4.6 cm (range: 1.8–16 cm). Prior to receiving NAC, 68% (n=27) of the patients were diagnosed with triple-negative breast cancer (TNBC), and 85% (n=34) had clinical T2 or T3 stage tumors, with 65% (n=26) classified as

Table 1 Clinicopathological Characteristics and Treatment

Age, Median (range), years	44(27–70)
Characteristic	n (%)
cT stage at presentation	
cT0	1(3%)
cT1	1(3%)
cT2	21(53%)
cT3	13(33%)
cT4	4(10%)
cN stage at presentation	
cN0	3(8%)
cN1	24(60%)
cN2	10(25%)
cN3	3(8%)
Clinical stage	
I	0(0%)
II	14(35%)
III	26(65%)
Tumor type	
Pure metaplastic carcinoma	10(25%)
Mixed metaplastic and NST	30(75%)
Metaplastic histologic subtype	
Matrix-producing	10(25%)
Squamous cell carcinoma	22(55%)
Spindle cell carcinoma	4(10%)
With mixed metaplastic elements	4(10%)
Receptor status	
TNBC	27(68%)
HR+(>10%)/HER2−	9(23%)
HER2 +	4(10%)

(*Continued*)

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Table 1 (Continued).

Preoperative chemotherapy	
NAC	33(82%)
NAC+Immunotherapy	7(18%)
Ki67	
Mean	54%
Low(<20%)	1(3%)
High(≥20%)	39(97%)
Type of surgery	
BCS	3(8%)
Mastectomy	37(93)%

Abbreviations: HR, hormonal receptor; TNBC, Triple-Negative Breast Cancer; NAC, neoadjuvant chemotherapy; NST, no special type; BCS, breast conserving surgery.

clinical stage III. The median Ki-67 proliferation index was 54% (range: 5–90%), with 97% (n=39) of patients showing a Ki-67 index of ≥20%.

Overall Efficacy of NAC and Immunotherapy

Out of the 40 patients, 33 received NAC alone, while 7 received NAC combined with immunotherapy. Among the 33 patients who underwent NAC alone, only 2 (6%) achieved a pCR (Figure 2). In contrast, of the 7 patients who received combined immunotherapy, 3 had immunotherapy initiated at the beginning of treatment, and 2 of these (67%) achieved pCR. The remaining 4 patients experienced disease progression during NAC but exhibited varying degrees of response after the addition of immunotherapy, ranging from stable disease (SD) to partial response (PR) (Figure 3). The detailed regimens for the 7 patients are presented in Table 2.

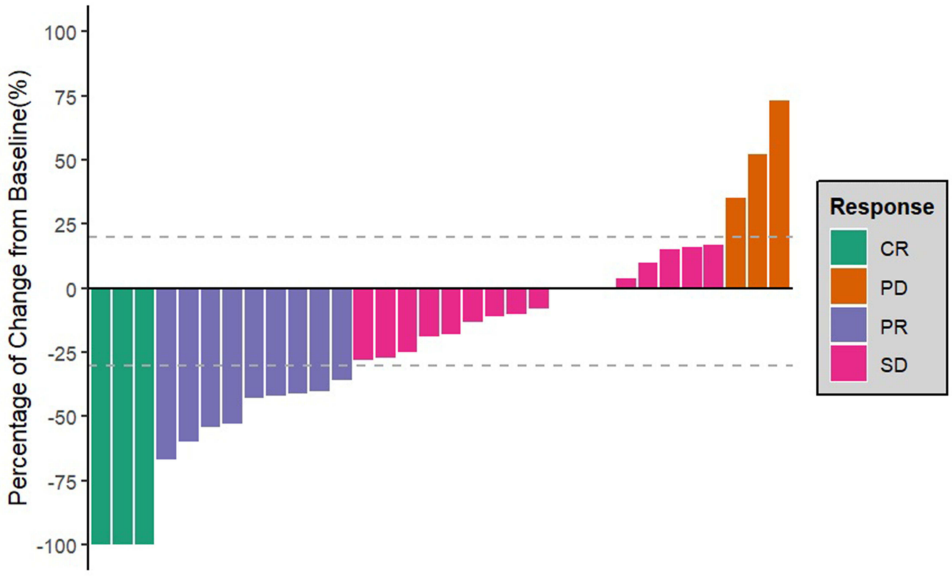

Figure 2 Bar chart showing the percentage of change from baseline in tumor response to neoadjuvant chemotherapy before and after the addition of PD-1 inhibitors. Each case includes two bars: the red bar represents the tumor response before the addition of PD-1 inhibitor, while the green bar represents the response after the PD-1 inhibitor was added. For cases 1 to 3, there is no red bar as these patients received PD-1 inhibitor from the beginning of chemotherapy, so there was no baseline phase without PD-1 treatment. In case 7, no red bar is shown because the baseline tumor measurement was zero. The dotted lines indicate the baseline (0%), the 20% increase for progression, and the 30% decrease for partial response.

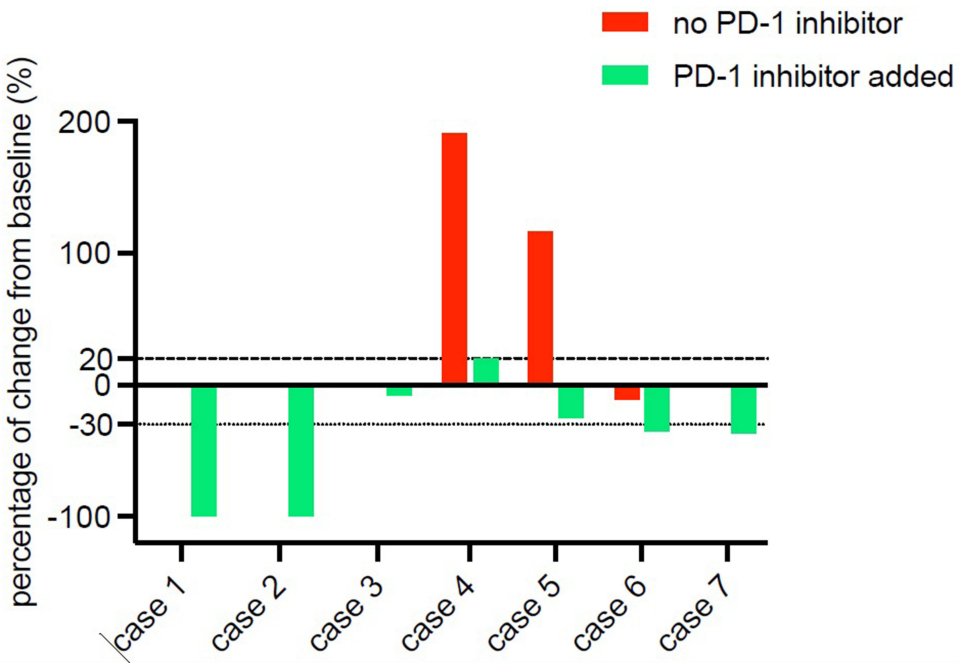

Figure 3 Percentage of Change from Baseline in Tumor Response Classified by RECIST Criteria. This waterfall plot illustrates the percentage change in tumor size from baseline for each patient, classified according to the RECIST (Response Evaluation Criteria in Solid Tumors) guidelines. Each bar represents an individual case, with different colors indicating response categories: complete response (CR, green), partial response (PR, purple), stable disease (SD, pink), and progressive disease (PD, Orange). The horizontal dashed lines denote the thresholds for PD (+20%) and PR (−30%). Cases with tumor shrinkage beyond −30% are classified as PR, while those with tumor growth exceeding +20% are considered PD. Cases falling between these thresholds are classified as SD, and those with complete tumor disappearance are categorized as CR.

Surgical and Pathological Evaluation

All patients underwent surgery following chemotherapy. Of these, 37 patients (92.5%) received a mastectomy with axillary lymph node dissection (ALND), and 3 successfully underwent breast-conserving surgery (BCS). Out of the 40 patients, 4 (10%) achieved pCR after NAC, including 3 patients with clinical stage II and 1 patient with clinical stage III. Additionally, 1 patient achieved pCR in the breast tissue but had residual metastatic disease in the axillary lymph nodes.

Overall pCR Performance

In total, 4 patients (10%) from the entire cohort achieved pCR, consistent with the low pCR rates reported in other studies on MpBC. Achieving pCR was associated with earlier clinical stages, suggesting that combining NAC with immunotherapy may be more effective in patients with early-stage disease.

Table 2 Tumor Size; Patient Age; and Neoadjuvant Treatment Regimens

Case	Age	Tumor Size at Diagnosis(cm)	Neoadjuvant Treatment Regimen
1	30	3.3	TCb*4-EC*4+Pembrolizumab*8
2	43	3.8	TCb*6+Tislelizumab*6
3	50	12	AC*4-T*2+Camrelizumab*6
4	53	6.4	AC*3 following T+Toripalimab*3
5	66	5.1	ddEC*4-TP*2 following Toripalimab*3
6	43	3.8	EC*2-TP*2 following T*4+Toripalimab*4
7	55	4.6	AC*4 following T*+Tislelizumab*4

Abbreviations: T, paclitaxel; Cb, carboplatin; E, epirubicin; A, doxorubicin; P, cisplatin; C, cyclophosphamide.

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Discussion

Metaplastic breast carcinoma (MpBC) is a rare and highly heterogeneous subtype of breast cancer, often presenting with larger tumors and a poorer response to standard therapies, including neoadjuvant chemotherapy (NAC).[22–24] Consistent with previous studies,[8,9,11–15] our findings confirm the low pathological complete response (pCR) rate in MpBC when treated with NAC alone. In our cohort, only 6% of patients achieved pCR following NAC without immunotherapy, highlighting the limited efficacy of chemotherapy in this subtype.

However, the addition of immune checkpoint inhibitors (ICIs) to NAC in our study led to a notable improvement in pCR rates, particularly in patients with early-stage disease. Among the 7 patients who received immunotherapy, 3 had immunotherapy initiated at the beginning of treatment, and 2 of 3 (67%) achieved pCR. This suggests that combining NAC with immunotherapy may enhance the tumor's response, aligning with findings from studies such as the KEYNOTE-522 trial, which demonstrated improved pCR rates and OS in TNBC with the addition of pembrolizumab.[25–27]

MpBC shares several characteristics with TNBC, including a lack of hormone receptor expression and HER-2 negativity, which may explain its potential responsiveness to immunotherapy. Studies have shown high levels of PD-L1 expression[28–30] and increased tumor-infiltrating lymphocytes (TILs)[31] in MpBC, most research suggests that elevated PD-L1 expression correlates with higher pathological complete response (pCR) rates and improved prognosis.[32] Additionally, the presence of TILs, particularly CD8+ lymphocytes, has been linked to better responses to immunotherapy in various cancers, including TNBC,[33] further supporting the use of ICIs in this subtype. Our results suggest that patients with earlier clinical stages (stage II) may benefit the most from this approach, as evidenced by the higher pCR rates observed in this group.

Patients with MpBC often present with advanced tumor stages and larger tumor sizes at diagnosis. In our study, the average maximum tumor diameter at presentation was 5.3 cm, and most patients were not eligible for BCS. Only 3 out of 40 patients (7.5%) opted for BCS. Among the 7 patients who received immunotherapy, one successfully underwent BCS with negative margins and achieved a pathological complete response (pCR). Previous studies have reported the feasibility and safety of BCS in patients with clinical T3–T4 breast cancer following neoadjuvant chemotherapy, challenging the traditional preference for mastectomy in this subgroup. Given the promising response to immunotherapy observed in our study, it raises the question of whether more patients could become eligible for BCS while maintaining oncologic safety and achieving better cosmetic outcomes. However, further research is needed to explore this possibility.

The observed pCR rate of 28.6% (2/7) with neoadjuvant immunotherapy in MpBC surpasses historical chemotherapy rates (5–10%),[9] yet remains lower than HER2+ breast cancer (50–70% with anti-HER2 therapy[34] and non-metaplastic TNBC (60–70% in KEYNOTE-522.[18] While direct cross-trial comparisons are confounded by biological heterogeneity, these contrasts emphasize the need for subtype-tailored strategies. Our findings provide the first benchmark for immunotherapy efficacy in MpBC, distinct from conventional TNBC paradigms.

The clinical significance of these findings is substantial. Achieving pCR has been associated with improved long-term outcomes, including better survival rates.[27,35,36] Thus, incorporating immunotherapy into the neoadjuvant setting for MpBC could represent a promising therapeutic strategy, particularly for early-stage patients.

Our study is a retrospective analysis. Due to the rarity of patients with metaplastic breast carcinoma (MBC) and the diagnostic challenges associated with preoperative needle biopsy, the number of cases in our study is relatively small, making it difficult to standardize chemotherapy regimens. Further prospective studies are warranted to confirm these findings and explore the full potential of immunotherapy in MpBC. While the KEYNOTE-522 study has demonstrated the efficacy of immunotherapy in TNBC, not all metaplastic carcinomas are TNBC, and this subgroup has not been specifically analyzed. Our study provides preliminary evidence supporting the use of ICIs in combination with NAC as a viable treatment option for improving outcomes in this rare and aggressive breast cancer subtype.

Conclusion

In conclusion, our real-world, single-center data provide detailed insights into the treatments received by nonmetastatic MpBC patients. We found that combining neoadjuvant chemotherapy (NAC) with immunotherapy may improve the pCR rate and may lead to better treatment outcomes, particularly in patients at relatively early stages.

Data Sharing Statement

The datasets generated during and analysed during the current study are not publicly available due to ethical concerns, the data used in this study cannot be made publicly available, but are available from the corresponding author on reasonable request.

Ethical Approval

This study received approval from the Institutional Review Board of Sun Yat-sen University Cancer Center.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest relevant to this article. This paper has been uploaded to ResearchGate as a preprint: https://www.researchgate.net/publication/386386000_Promising_Response_to_Neoadjuvant_Chemotherapy_Plus_Immunotherapy_in_Metaplastic_Breast_Carcinoma

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