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BRIEF REPORT

Lack of efficacy to systemic chemotherapy for treatment of metaplastic carcinoma of the breast in the modern era

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Abstract Metaplastic carcinoma of the breast (MCB) is a rare subtype of breast cancer. Anecdotal reports are available regarding its response to systemic chemotherapy. We reviewed the records of patients diagnosed with MCB at National Taiwan University Hospital between 1988 and 2009. A total of 46 MCB cases were identified from 8,695 breast tumor patients who underwent biopsy or resection. About 11 of 25 patients with initial bulky disease (T3-4) received neoadjuvant chemotherapy before surgery, and 2 (18.2%) exhibited a partial response. About 12 of 18 patients who developed distant metastasis received palliative systemic chemotherapy. Of them, only 1 (8.3%), 1 (10%), and none (0%) responded to first-, second-, or third- and beyond line chemotherapy, respectively. None of the patients who received anthracyline- ($n = 13$), vinorelbine- ($n = 7$), or cyclophosphamide-based ($n = 18$) chemotherapy responded, whereas 3 (17.6%) of 17 patients who received taxane-based chemotherapy exhibited a partial response. Tumor response to systemic chemotherapy remains generally poor for MCB patients. Taxanes may have modest activity, but need to be validated in further studies.

Keywords Metaplastic carcinoma of breast · Neoadjuvant chemotherapy · Chemotherapy

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Introduction

Metaplastic carcinoma of the breast (MCB) is a rare subtype of breast cancer, accounting for less than 1% of cases of breast cancer [1–3]. MCB has both epithelial and mesenchymal components, and two to three different components may exist within the tumor simultaneously [4]. Several features indicate that MCB should be treated as a different entity from the relatively more common infiltrating ductal carcinoma (IDC). First, although composed of both epithelial and mesenchymal components, MCB has heterogeneous groups of cells. Second, the behavior of MCB is more similar to that of a low-grade sarcoma with cells of mesenchymal origin rather than IDC.

Compared with major IDC of the breast, MCB is more likely to present with locally advanced disease and poorer prognosis [5]. Therefore, multimodal treatment is frequently used for MCB patients both at disease presentation and at disease recurrence. However, the efficacy of

systemic chemotherapy and the optimal regimens for MCB remains unknown. In clinical practice, MCB is usually treated according to the guidelines developed for IDC [6], and a poor response to conventional chemotherapy has been reported by the authors of previous case series [7–9]. In Hennessy's report [7], only a 10% pathologic complete response rate was ever reported for some of their patients who received neoadjuvant chemotherapy between 1985 and 2001 at the MD Anderson Cancer Center. Prospective clinical trials specifically focused on MCB are difficult to conduct because of its rarity and heterogeneous histological characteristics.

In light of the newer therapeutic agents in the armamentarium for breast cancer treatment, this study aimed to characterize the chemotherapy response of MCB patients in neoadjuvant settings for locally advanced disease and palliative settings for metastatic disease. Potential predictors of treatment efficacy are explored.

Patients and methods

The study was approved by the Research Ethics Committee of the National Taiwan University Hospital. *Metaplastic carcinoma of breast cancer* was used as a keyword to identify patients from the cancer registry of the Medical Information Management Office and the Department of Pathology in NTUH. Patients with stages I–IV disease who had undergone biopsy or surgery for MCB from January 1988 to December 2009 were enrolled in this study. The charts and clinical data were reviewed.

Demographic data, treatment modalities, pathology findings, chemotherapy regimens, radiotherapy, best response to treatment, and survival were reviewed. The response was evaluated by primary physicians using the Response Evaluation Criteria in Solid Tumors (RECIST) [10] rather than by the author.

The primary interest was the treatment outcome, including the response rate to systemic chemotherapy and survival. Overall survival (OS) was defined as the time (in months) from the start date of the given treatment regimen to the date of death. For patients who did not die, survival duration was censored at the last date the patient was known to be alive. Time to tumor progression (TTP) was defined as the time (in months) from the start date of the given treatment regimen to disease progression, death, or change of treatment regimens, whichever came first.

For each given treatment regimen (cytotoxic/targeted therapy), the best response was summarized. The best response rate was defined as the number of patients whose best response was CR or PR during the treatment divided by the number of patients with measurable disease under the treatment with evaluable response.

Statistics

Descriptive statistics was used to summarize the patients' characteristics and treatment history. Data on response rates were compared using the chi-square test for categorical variables or two-tailed Fisher's exact test if the expected number of each cell was less than five cases.

The Kaplan–Meier method was also used to estimate the probabilities of survival. The log rank test was used for univariate comparisons. All statistical analyses were performed with the statistical package SPSS for Windows (Version 17.0, SPSS Inc, Chicago, IL).

Results

Patients' characteristics

A total of 46 MCB patients were identified from 8,695 breast tumor patients undergoing biopsy or resection at our hospital from January 1993 to December 2009 (Table 1). The clinical characteristics of these patients were similar to those of others reported previously [5]. The most common single metaplastic component was squamous cell carcinoma (26.1%), and 18 of the patients (39.1%) had more than one type of metaplastic component within their tumors.

For the 43 patients with loco-regional diseases at presentation, mastectomy was performed in 36 and breast-conserving surgery was performed in 7. Neoadjuvant chemotherapy was administered to 12 patients. About 24 patients received adjuvant chemotherapy, and 11 received adjuvant radiotherapy. Of the 3 patients with distant metastasis at initial presentation, 2 underwent mastectomy before palliative chemotherapy. As of December 31, 2009, the median follow-up time of the entire group of patients was 30.2 months (95% C.I. 5.3–192.6 months).

A total of 18 patients received chemotherapy in either neoadjuvant or metastatic settings. The three most commonly used chemotherapeutic regimens in these settings were cyclophosphamide/epirubicin/fluorouracil or cyclophosphamide/epirubicin ($n = 11$, 61.1%), taxane (docetaxel or paclitaxel)/cisplatin ($n = 5$, 27.8%), and paclitaxel/24-hour infusional fluorouracil/leucovorin ($n = 2$, 11.1%).

Outcomes of patients receiving neoadjuvant chemotherapy

For the 12 patients who received neoadjuvant chemotherapy (Table 2, patient numbers 1–12), 2 had PR and 10 had PD. The 2 responders were treated with docetaxel/cisplatin and weekly paclitaxel/24-h high-dose infusional fluorouracil/leucovorin, respectively. Eleven of these patients underwent

Table 1 Patient demographics

	$N = 46$	%
Age (median/range)	53.5 years	(35–84 years)
Gender (M/F)	1/45	
Initial T3/T4 tumor	25	54.4
Metastases at presentation	3	6.5
Distant metastases later	15	32.6
ER (+)	5	10.9
PR (+)	10	21.7
HER2/neu (+)	2	4.3
Triple negative	29	63.0
Metaplastic component		
SpCC	8	17.4
SCC	12	26.1
C	1	2.2
Chondromyxoid	1	2.2
S	5	10.9
Mixed	18	39.1
Cartilagenous/osteoid	1	2.2
SCC/SpCC	3	18.8
SCC/C	1	2.2
SCC/chondroid	1	2.2
SCC/S	2	4.3
SpCC/S	2	4.3
SpCC/anaplastic	1	2.2
SpCC/cartilagenous	1	2.2
SpCC/cartilagenous/osseous	1	2.2
SpCC/chondroid	1	2.2
SpCC/S/epithelioid	1	2.2
SpCC/epithelioid	2	4.3
Fibromyxoid/chondro-osteoid	1	2.2
Unknown	1	2.2

C Chondrosarcoma, *ER* estrogen receptor, *PR* progesterone receptor, *S* sarcomatous, *SCC* squamous cell carcinoma, *SpCC* spindle cell carcinoma

modified radical mastectomy after neoadjuvant chemotherapy. Three of them were still alive without recurrence at the time of this study, but none of these 3 survivors exhibited a response to neoadjuvant chemotherapy.

Outcomes of patients receiving palliative chemotherapy

Eighteen MCB patients (39.1%) developed metastatic disease at initial presentation or during follow-up after primary treatment. Of them, 12 received systemic chemotherapy. The disease status, chemotherapy regimens, and response details of these 12 patients are tabulated in Table 2 (patient numbers 7–18). Only 2 patients (16.7%) had PR, and all the other 10 patients (83.3%) experienced PD. One of the patients who had PR received weekly paclitaxel and 24-h high-dose infusional fluorouracil/leucovorin treatment. The other patient was treated with oral uracil-tegafur for 8 months before disease progression.

Predictors of the effectiveness of chemotherapy

A total of 18 patients received chemotherapy in either neoadjuvant or palliative settings. Only 4 responded to at least one chemotherapeutic regimen. Among the responders ($n = 4$) and non-responders ($n = 14$), metaplastic components with squamous cell carcinoma ($P = 0.584$, Fisher's exact test) or spindle cell carcinoma ($P = 1.000$), ER positivity ($P = 1.000$), PR positivity ($P = 1.000$), or HER-2 positivity ($P = 0.426$) did not contribute to any significant differences. The median time from diagnosis of metastatic disease to death was 10.65 months (10.65 and 5.29 months for those who had and had not received palliative chemotherapy, respectively, log rank $P = 0.616$). Median TTP of first-line chemotherapy for metastatic MCB treated using taxane-based and non-taxane-based therapies were 1.55 and 0.73 months ($P = 0.961$), respectively.

Effectiveness of chemotherapy regimens

Treatment regimens were categorized according to treatment backbone, timing, and response as outlined in Table 3. Taken together, 18 patients received a total of 89 chemotherapy regimens during treatments. No patient responded to anthracyline- ($n = 13$), vinorelbine- ($n = 7$), or cyclophosphamide-based ($n = 18$) regimens. Three out of 17 patients who received taxane-based chemotherapy had PR (17.6%).

Discussion

According to our single-institute retrospective study, the response of MCB to systemic chemotherapy remains poor in the modern era. Ninety percentage of patients who received neoadjuvant chemotherapy experienced disease progression. The response rate to chemotherapy in metastatic MCB was as low as 16.7%, whereas that in metastatic IDC was reported to be between 21 and 75% [11]. There are only a limited number of reports regarding the efficacy of neoadjuvant chemotherapy for MCB. In our series, the response to neoadjuvant chemotherapy was quite poor, and all three patients who are still alive today did not respond to neoadjuvant chemotherapy at all. Therefore, in MCB patients with operable large tumors, immediate surgery rather than neoadjuvant chemotherapy should be recommended.

There are three case series describing neoadjuvant or palliative chemotherapy in patients with MCB [7–9].

Table 2 Characteristics of patients undergoing systemic chemotherapy

Pt	Age	Sex	TNM	Initial staging	Metaplastic component	ER	PR	HER-2	Neoadjuvant regimens
1	72	F	T4dN0M0	IIIB	Malignant fibromyxoid elements, malignant chondro-osteoid components	−	+	−	CEF(2)
2	46	F	T3N0M0	IIB	SpCC, some epithelial-like cells with necrosis	−	−	−	CEF(1)
3	70	F	T3N2M0	IIIA	S. (mainly with increased mitosis, cell pleomrophism) + focal carcinoma nests	−	−	−	CEF(3), TE(2)
4	50	F	T3N2M0	IIIA	SpCC,anaplastic cells	−	−	−	DP(4)
5	44	F	T4N3M0	IIIc	SCC, S.	−	−	−	TP (3)
6	62	F	T4dN0M0	IIIB	Carcinosarcoma	+	−	NA	CEF(2)
7	48	F	T2N3M0	IIIC	S	−	−	−	CEF(3)
8	47	F	T3N0M0	IIB	SCC, chondrosarcomatous component	−	−	−	CEF(2),DP(3), X(1 m), N-FL(1)
9	49	F	T3N2M0	IIIA	SpCC/cartilaginous/osseous metaplasia	+	+	−	DXP(2)
10	55	F	T3N1M1	IV	SCC	−	+	−	CEF(2), TP(2)
11	53	F	T3N0M0	IIB	S/SpCC and matrix	−	−	−	TEC(4)
12	57	F	T4N2M0	IIIB	SCC	−	−	+	T-FL
13	37	F	T3N2M0,	IIIa	SpCC, S	−	−	−	
14	43	F	T3N0M0	IIB	SpCC/chondroid differentiation	−	−	−	
15	63	F	T2N0M0	IIA	Epithelial/SpCC	+	−	−	
16	72	F	T4NxM0	IIIB	SCC	+	+	−	
17	55	F	T3N0M0	IIB	S	−	−	−	
18	39	F	T3NxM1,	IV	SCC	−	−	+	

Pt	Age	Sex	Neoadjuvant best response	Metastatic sites	Palliative regimens	Best response	Survival	Survival after mets	OS (months)
1	72	F	PD	Nil			Y	NA	138.4
2	46	F	PD	Nil			Y	NA	103.1
3	70	F	PD	Nil			Y	NA	111.1
4	50	F	PR	Nil			N	NA	19.1
5	44	F	PD	Nil			N	NA	15.4
6	62	F	PD	Nil			Y	NA	62.0
7	48	F	PD	Liver	NP, UFUR/P	PD	N	2.9	10.8
8	47	F	PD	Lung, brain	Oral C/E'	PD	N	11. 6	25.9
9	49	F	PD	LN,	CEF, A + MMC, cetuximab, H	PD	N	10.6	13.2
10	55	F	PD	LN, lung, bone	N-FL, A + IE', A + M' + MMC,G	PD	N	11.9	11.9
11	53	F	PD	Brain, lung, bone, gingival, abdominal	Imatinib	PD	N	2.0	17.5
12	57	F	PR	Lung, bone, chest wall	T-FL, H-N-FL, CE, TGH	PD	N	9.0	25.1

Table 2 continued

Pt	Age	Sex	Neoadjuvant best response	Metastatic sites	Palliative regimens	Best response	Survival	Survival after mets	OS (months)
13	37	F		Chest wall, Lung, LN, liver, pleural effusion, bone, brain	CMF, CEF, M'NP	PD	N	7.00	12.6
14	43	F		Lung, bone, brain	UFUR*	PR	N	12.4	104.5
15	63	F		Lung/hilar/LV myocardium/tumor emboli in PV/LA, brain	EC, DP	PD	N	2.7	10.3
16	72	F		Supraclavicular LN, lung	CMF, T-FL*	PR	N	2.7	5.9
17	55	F		Lung, chest wall/liver/ subcutaneous soft-tissue mass, mediastinal invasion.(+)	NX	PD	Y	21.6	56.8
18	39	F		LN, Bone, Lung, skin	H-T, H-T-FL, CE, NP, Capecitabine/ Lapatinib, TGH, oral E' + M, DH, DPH, E–H, oral C, VMH, V, H-CMF	PD	N	34.4	34.4

A bevacizumab, *C* cyclophosphamide, *D* docetaxel, *E* epirubicin, *E′* etoposide, *F* Fluorouracil, *FL* high-dose fluorouracil + leucovorin, *G* gemcitabine, *H* trastuzumab, *I* ifosfamide, *M* methotrexate, *M′* mitoxantrone, *Mets* Metastases, *MMC* mitomycin C, *N* vinorelbine, *P* cisplatin, *S* Sarcomatoid, *SCC* squamous cell carcinoma, *SpCC* spindle cell carcinoma, *T* Paclitaxel, *V* Vinblastine, *X* capecitabine

* Regimens with response

Table 3 Chemotherapy Regimens in Summary

Regimens		Treatment lines			Clinical response			Regimens in PR	Response rate (RR)
		First	Second	Third and beyond	PR	SD	PD		PR/total number (RR%)
T/D-based	Neoadjuvant	5	3	0	2	0	6	DP, T-HDFL	3/17 (17.6)
	Palliative	2	3	4	1	0	8	T-HDFL	
E/A-based	Neoadjuvant	6	1	0	0	0	7		0/13 (0.0)
	Palliative	3	2	1	0	0	6		
Cisplatin-based	Neoadjuvant	3	2	0	1	0	4	DP	1/10 (10.0)
	Palliative	1	2	2	0	0	5		
Vinorelbine-based	Neoadjuvant	0	0	1	0	0	1		0/7 (0.0)
	Palliative	3	1	2	0	0	6		
5FU-based	Neoadjuvant	9	0	2	1	0	10	T-HDFL	3/25 (12.0)
	Palliative	7	5	2	2	0	12	UFUR, T-HDFL	
Cyclophosphamide based	Neoadjuvant	8	0	0	0	0	8		0/18 (0.0)
	Palliative	5	1	4	0	0	10		

5-FU Fluorouracil, *A* doxorubicin, *E* epirubicin, *D* docetaxel, *HDFL* high dose fluorouracil/leucovorin, *PD* progressive disease, *PR* partial response, *SD* stable disease, *T* paclitaxel, *UFUR* uracil-tegafur

Luini's study reported that 3 of 37 patients received neoadjuvant chemotherapy, but their responses were not reported. In Rayson's series, taxane was not as popular as a frontline treatment. One PR was observed from ten different regimens for metastatic MCB, but only one of the seven patients received taxane-based chemotherapy. Hennessy and colleagues [7] demonstrated a 10% pathologic CR rate in neoadjuvant patients, all of whom received four to six cycles of 5-fluorouracil/doxorubicin/cyclophosphamide (FAC). In our series, all patients receiving anthracycline had epirubicin rather than doxorubicin in their regimens. The average treatment intensity of epirubicin was 68.3 mg/m^2 (50–100 mg/m^2) per cycle. In terms of a comparative dose of 1.5:1 of epirubicin and doxorubicin, the antitumor efficacy of epirubicin and doxorubicin was found to be equivalent in cases of breast cancer [12–14], lymphoma [15], and soft-tissue sarcoma [16]. Therefore, the majority of doxorubicin responders in Hennessy's study and epirubicin non-responders in our series might be a result of either coincidence or insufficient epirubicin dosage. However, whether MCB responded to doxorubicin and epirubicin differently remains unknown. In addition, taking together the cases from Rayson's [9] and our series, 3 (12.5%) of 24 and 2 (15.4%) of 13 patients responded to first- and second-line chemotherapy, respectively. No patient (0/7, 0%) responded to third-line chemotherapy or beyond. Only one (5.6%) of 18 patients receiving anthracycline-based regimens exhibited a clinical response. No patient responded to vinorelbine- ($n = 7$) or cyclophosphamide-based ($n = 28$) regimens. Therefore, MCB generally responded poorly to commonly used chemotherapeutic agents, except taxane and doxorubicin. Although taxanes only elicited a modest response rate (17.6%) in our series, they should not be omitted from the frontline options of traditional chemotherapy for MCB patients. Median TTP of first-line treatment in our patients with taxane and non-taxane treatments was 1.55 and 0.73 months, respectively, whereas that of metastatic IDC of the historical control [17] between 1998 and 2007 was 7.8 months. Because of the generally low response rate in MCB patients and limited sample size, TTP differences between taxane and non-taxane therapies might not occur.

The poor response to systemic chemotherapy and occasional long-term survival after loco-regional therapy might imply similar clinical behavior of MCB and low-grade sarcoma. Brown-Glaberman and colleagues described one successful PR in a metastatic MCB patient treated with ifosfamide and etoposide. Chien's report [18] also demonstrated that nearly CR with neoadjuvant chemotherapy with bevacizumab/doxorubicin/dacarbazine for the sarcomatous part in MCB, followed by gemcitabine/paclitaxel for the IDC part. While taxane and doxorubicin showed better efficacy in ours and others' series, the two groups of agents are also effective for treating soft-tissue sarcoma [19]. On the other hand, Moulder et al. [20] treated patients with metastatic MCB with bevacizumab/temsirolimus/liposomal doxorubicin and also shed some light on the treatment response. Although these are three sporadic case reports, these effective regimens taken together prompted us to reconsider the concept of treating MCB as a sarcoma-like entity.

Our study has many limitations, such as small sample size, retrospective design, and the fact that it is a single-institute study. However, our patient characteristics were

comparable to that from the National Cancer Database containing 892 patients [5], implying that the conclusion should still be representative. A prospective study or investigational study for newer treatment standards should be conducted.

In conclusion, the response of MCB patients to systemic chemotherapy remains poor despite the advancements in chemotherapy since 2000. Taxane- or doxorubicin-containing regimens might be the two major categories of traditional chemotherapeutic agents worth recommending. Innovative or investigational treatment should be explored for MCB patients.

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