Clinical analysis of metaplastic breast carcinoma with distant metastases: A multi-centre experience

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Abstract. Metaplastic breast cancer (BC-Mp), which includes a range of epithelial and mixed epithelial-mesenchymal tumours, are rare malignancies with an unfavourable prognosis. The limited literature on BC-Mp focuses mainly on retrospective data for radically treated patients. Notably absent are studies dedicated to the palliative treatment of BC-Mp with distant metastases. The present retrospective study investigated treatment modalities and prognosis in a multi-centre cohort of 31 female participants diagnosed with distant metastatic BC-Mp, including 7 patients with *de novo* metastatic disease. The median age of the patients was 61 years (range, 33-87 years), with 38.7% presenting local lymph node involvement. Lungs were the most common site for the metastatic disease (61.3%). Median Ki-67 index was 50% (range, 35-70%), and 80.7% of cases were classified as grade 3. Human epidermal growth factor receptor 2 $(HER2)^+$ and estrogen $receptor^+$ were detected in 12.9 and 6.5% of cases, respectively. A total of 62.4% of patients received first-line palliative systemic treatment. The 1- and 2-year overall survival (OS) were 38.5 and 19.2%, respectively. Receiving ≥1 line of palliative treatment was significantly associated with improved OS (P<0.001). Factors such as age, Ki-67 index, HER2 or hormonal status, presence of specific epithelial or mesenchymal components, location of metastases or chemotherapy regimen type did not influence OS. The present study provided insights into the clinicopathological profile, systemic treatment experience, prognostic factors and OS data of BC-Mp with distant metastases, emphasizing the imperative for clinical trials in this population.

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Abbreviations: BRCA1, breast cancer gene 1; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; BC, breast cancer; mBC, BC with distant metastasis; BC-Mp, metaplastic BC; mTOR, mammalian target of rapamycin; OS, overall survival; PFS, progression free survival; NST, no special type; ORR, objective response rate; PARPi, poly ADP-ribose polymerase inhibitor; PD-L1, programmed death ligand 1; PI3K, phosphoinositide 3-kinase; PrR, progesterone receptor; SD, standard deviation; TROP-2, trophoblast cell surface antigen-2; VIF, variance inflation factor

Key words: metaplastic breast cancer, metastasis, chemotherapy, systemic treatment, overall survival

Introduction

Breast cancer (BC) remains the foremost cause of mortality in women worldwide (1). Advanced BC encompasses both locally advanced BC that is inoperable and BC that has metastasized to distant sites (mBC) (2). The majority of breast malignancies arise from epithelial components, with ductal carcinoma [no special type (NST)] being the most prevalent (3). Lobular carcinoma accounts for ~8% of cases, whilst less common subtypes such as metaplastic (BC-Mp), medullary, neuroendocrine, tubular and mucinous carcinomas make up 1-2% of cases (3). BC is classified into several subtypes, including Luminal A, Luminal B, human

epidermal growth factor receptor 2 (HER2)$^+$ and basal-like (with triple-negative being the most common). These classifications are determined by the expression of estrogen receptor (ER), progesterone receptor (PrR), Ki-67 status and HER2 status (4).

BC-Mp, encompassing both epithelial and mixed epithelial-mesenchymal tumours, are more likely to be triple-negative and generally demonstrate a less favourable prognosis when compared with triple-negative invasive ductal carcinoma (5-7). BC-Mp has been reported to have low chemosensitivity according to certain studies (8-10). There is controversy, particularly regarding prognostic factors and treatment guidelines, owing to its diverse nature and rarity. A notable number of patients diagnosed with localized disease face dissemination or local recurrences (8-10). Data on outcomes of palliative treatment regimens used in this setting are limited with the majority of publications concentrating on the following: i) Clinicopathological characterisations with no or insufficient data regarding palliative treatment (11-19); ii) a small number of patients with mBC-Mp (20,21); iii) radical treatment outcomes (22-24); or iv) data from the general population without further details on mBC-Mp (9,25,26).

The objective of the present study was to evaluate overall survival and factors influencing it in patients with mBC-Mp who received treatment at four Cancer Reference Centres/University Hospitals located in Southern and Central Poland, and to establish clinicopathological group characteristics.

Materials and methods

Patients and data extraction. Patients diagnosed with BC-Mp between 2012-2022 were identified using the registry systems of four medical units: The Maria Sklodowska-Curie National Research Institute of Oncology, Branch in Warsaw, Krakow and Gliwice, Poland, and the Department of Oncology at the University Hospital in Krakow, Poland. The imaging results for patients with BC-Mp were reviewed to identify a subset of individuals undergoing palliative treatment.

The inclusion criteria of the study encompassed individuals with a confirmed diagnosis of BC-Mp in either postsurgical or core biopsy pathology reports, along with evidence of dissemination on imaging studies. The typical method for determining the diagnosis of BC-Mp involved a combination of morphological evaluation and immunohistochemical staining (27). There were no restrictions based on the sex or age of the patients. Patients lacking an original pathology report or those concurrently experiencing active malignancies were excluded from the study.

Information pertaining to age and sex, as well as clinical details such as tumour location and size, local lymph node involvement, location of distant metastatic disease, dates and types of palliative systemic treatment, the initial treatment intention (palliative vs. radical) at the initial diagnosis of the patients, survival status, dates of the last visit and histopathological data (including histology, ER, PrR, HER2, Ki-67 status, presence of ductal carcinoma *in situ*, tumour grade and presence of different BC-Mp components) were collected retrospectively to ensure a comprehensive analysis.

Statistical analysis. All analyses were performed using R software, version 4.3.2 (The R Foundation). $P<0.05$ was used to indicate a statistically significance difference. The mean, standard deviation (SD), median, quartiles and range of quantitative variables were generated. For qualitative variables, the absolute and relative frequencies (n and %) were reported. Univariate and multivariate Cox regression (proportional hazards model) were used to model the potential impact of predictors on a time to event. Hazard ratios (HR) and 95% confidence intervals were generated. The choice of independent variables was based on their significance in the univariate analyses and so Events Per Variable was >10, or ≥5, where 10 was not reachable. Multicollinearity was assessed using the variance inflation factor (VIF). Predictors with VIF>5 were removed from the model.

Results

Population clinicopathological characteristics. The present research involved a cohort of 31 female participants, with no male subjects included. The median age at the time of mBC-Mp diagnosis was 61 years (quartiles, 50-69 years), and the mean age ± SD was 59.7±14.2 years (range, 33-87 years). mBC-Mp constituted <1% of the total breast cancer cases within each institution and 25.4% of all BC-Mp cases identified in all databases.

The median Ki-67 was 50% (quartiles, 35-70%) with a mean ± SD of 51.5±23.1% (range, 10-90%; n=29). The median tumour size was 70 mm (quartiles, 39.8-111.3 mm), and the mean ± SD was 73.4±35.8 mm (range, 20-130 mm; n=28). The most common site for distant metastatic disease were lungs (61.3%). Further clinicopathological data regarding patients are presented in Table I. All patients presented with distant metastases at the study entry and there were no patients presenting with inoperable BC-Mp that were receiving palliative treatment.

First-line systemic treatment. Overall, 20 patients (62.4%) received first-line palliative systemic treatment. The types of treatments applied in the first-line setting are presented in Table II. The proportion of patients that received systemic treatment in the first- to fifth-line of palliative therapy is presented in Fig. 1.

Median progression-free survival (PFS) in first-line treatment was 15.8 weeks (range, 3-84 weeks) with 8 patients (40%) responding to the treatment (at least stable disease). In second-line treatment, PFS was 7.5 weeks (range, 3-30) with 3/12 patients (25%) responding to the treatment, including two patients who were HER2$^+$ and received lapatinib and capecitabine, and one patient treated with a poly ADP-ribose polymerase inhibitor (PARPi; within a clinical trial). In third- and fourth-line treatments, 2/8 patients (with capecitabine, n=1; and with cisplatin-gemcitabine regimens, n=1) and ¼ patients responded to the treatment (with trastuzumab emtansine).

Overall survival. Up until July 2023, the median observation time was 7.4 months (range, 0.7-31.5 months). A total of 28/31 patients died (90.32%). Table III and Fig. 2 present the overall survival (OS) data.

Table I. Clinical and pathological characteristics of the patients (n=31).

Characteristic	n (%)
Lymph node involvement	
Positive	12 (38.7)
Negative	19 (61.3)
Distant metastases location-first metastatic site[a]	
Lung	19 (61.3)
Distant lymph node	6 (19.4)
Bone	4 (12.9)
Liver	4 (12.9)
Central nervous system	4 (12.9)
Skin and subcutaneous tissue	3 (9.7)
Other sites	5 (16.1)
Distant metastases location-all metastatic sites[a]	
Lung	19 (61.3)
Distant lymph node	7 (22.6)
Bone	5 (16.1)
Liver	4 (12.9)
Central nervous system	6 (19.4)
Skin and subcutaneous tissue	4 (12.9)
Other sites	5 (16.1)
Grade	
2	4 (12.9)
3	25 (80.6)
No data	2 (6.5)
DCIS presence	
Yes	7 (22.6)
No	23 (74.2)
Unknown	1 (3.2)
ER status	
Positive	2 (6.5)
Negative	29 (93.5)
PrR status	
Positive	0 (0.0)
Negative	31 (100.0)
Subtype	
Luminal A	0 (0.0)
Luminal B	2 (6.5)
HER2$^+$	4 (12.9)
Triple-negative	25 (80.6)
HER2	
Positive	4 (12.9)
Negative[b]	27 (87.1)
Type of component[c]	
NST	10 (32.3)
Squamous	16 (51.6)
Spindle cell/pleomorphic/sarcomatid	9 (29.0)
Osseous/chondroid	5 (16.1)
Mesenchymal unspecified	2 (6.4)
Lipid-rich	1 (3.2)
Menopausal status	
Premenopausal	11 (35.5)
Postmenopausal	19 (61.3)
Unknown	1 (3.2)
Comorbidities	
Yes	13 (41.9)
No	16 (51.6)
Unknown	2 (6.5)
Intention of treatment at initial diagnosis	
Radical	24 (77.4)
Palliative	7 (22.6)
Prior systemic treatment received	
Yes	19 (61.3)
No	12 (38.7)

[a]Can be >1 site; [b]IHC: HER2-0; HER2-1; HER2 IHC 2 and fluorescence *in situ* hybridization negative; [c]Any epithelial or mesenchymal component that was described in the histopathology report. IHC, immunohistochemistry; DCIS, ductal carcinoma *in situ*; ER, estrogen receptor; PrR, progesterone receptor; HER2, human epidermal growth factor receptor 2; NST, no special type.

Table II. Systemic treatment regiments received in a first-line setting (n=20).

First-line systemic treatment type[a]	n (%)
Anthracycline-based	8 (40.0)
Taxan-based	4 (20.0)
Platinum-based	7 (35.0)
Gemcitabine-based	2 (10.0)
Anti-HER2[b]	2 (10.0)
Anti-PD1[c]	1 (5.0)
CMF scheme	1 (5.0)
Hormonal agents[d]	1 (5.0)
Single agent therapy	12 (60.0)
Combination therapy	8 (40.0)

[a]Patient could receive >1 agent; [b]in HER2$^+$ patient; [c]within clinical trial; [d]in ER$^+$ patient. HER2, human epidermal growth factor receptor 2; PD-1, programmed cell death protein 1; CMF, cyclophosphamide, methotrexate and fluorouracil; ER, estrogen receptor.

Factors influencing overall survival. The univariate proportional hazards Cox models demonstrated that the likelihood of death at any given time was significantly reduced by 82.8% (HR=0.172) in individuals who received at ≥1 line of palliative treatment. Additionally, *de novo* diagnosis of disseminated disease significantly decreased the probability of death at any given time by 72.2% (HR=0.278) compared with patients previously treated with curative intent.

Table III. Overall survival data for patients with metaplastic breast cancer with distant metastases.

		Overall survival[a] (%), months			
Patients, n	Events (deaths), n	6	12	24	Median
31	28	56.67	38.46	19.23	7.36

[a]Defined as the time from diagnosis of metastatic disease to death (from any reason).

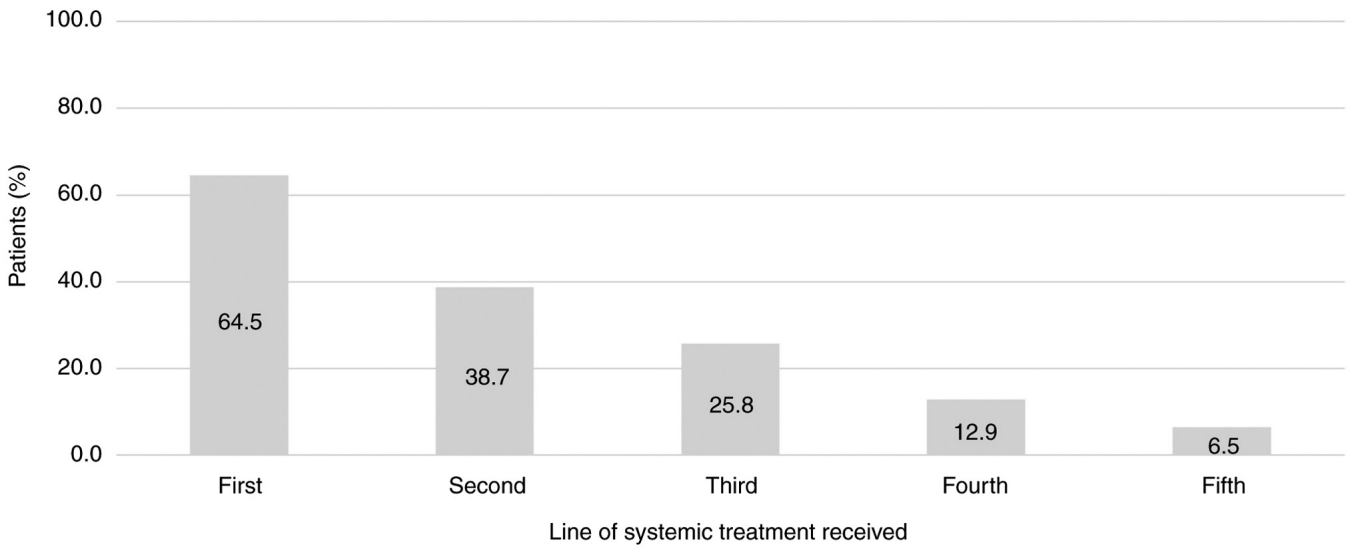

Figure 1. Proportion of patients with metastatic metaplastic breast cancer (n=31) receiving systemic first- to fifth-line treatment.

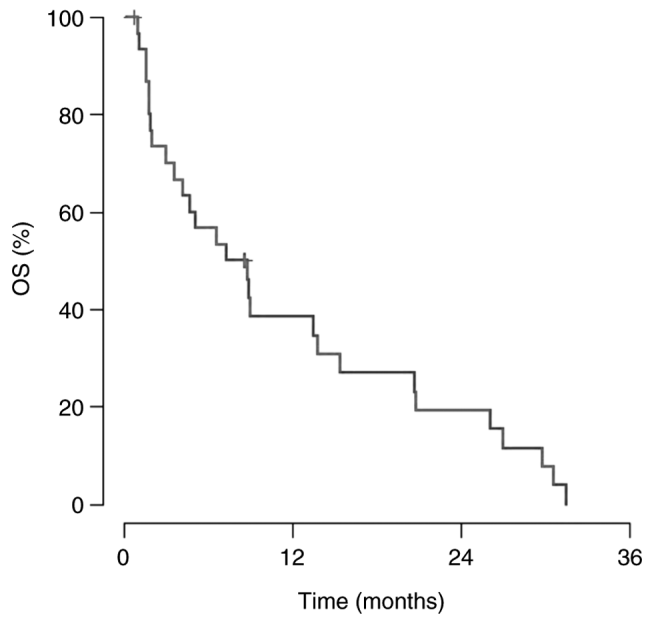

Figure 2. OS of patients with metastatic metaplastic breast cancer. OS, overall survival.

In the multivariate proportional hazards Cox model, application of ≥1 line of palliative chemotherapy significantly reduced the probability of death at any given time by 76.4% (HR=0.236). Furthermore, *de novo* diagnosis of mBC-Mp significantly decreased the likelihood of death at any given time by 72.3% (HR=0.277) in comparison with patients with secondary cancer dissemination. Factors such as comorbidities (requiring pharmacological treatment), presence of specific epithelial or mesenchymal components, location of metastases or chemotherapy regimen type did not influence OS. Table IV presents the outcomes of the univariate and multivariate proportional hazards Cox models.

Discussion

The present study presented clinical data for one of the largest cohorts of patients with mBC-Mp published and is second most extensive study thus far with regards to publications discussing treatment responses and the types of regimens used, to the best of our knowledge (28). The majority of patients presented as triple negative (TN)BC with poorly differentiated tumours aligning with the general trend in studies exploring BC-Mp clinicopathological data (Table V) (29). However, the population in the present study had even lower rates of ER^+/PrR^+ and $HER2^+$ in comparison with other cohorts, although there were certain studies reporting 100% or ≤100% of $HER2^-$ populations (11,30), and a sparse occurrence of ER^+ cases (22). The prognostic significance of $ER^+/(PrR^+)$ in a mBC-Mp population is uncertain, given that only two patients in the present study were ER^+. Other studies have not reported such prognostic relevance (31,32). In a cohort from Pakistan, the hormone-positive status was

Table IV. Outcomes of univariate and multivariate proportional hazards Cox models.

			Overall survival					
			Univariate model			Multivariate model		
Variable	Total, n	Deaths, n	HR	95% CI	P-value	HR	95% CI	P-value
Age	-	-	1.032	0.997-1.067	0.072	1.029	0.994-1.065	0.106
Menopause								
No	11	10	1	ref.	-			
Yes	19	17	1.078	0.486-2.388	0.854			
Histopathology performed in a reference centre								
No	11	10	1	Ref.	-			
Yes	20	18	1.887	0.776-4.590	0.162			
Grade								
2	4	4	1	ref.	-			
3	25	22	0.692	0.231-2.074	0.511			
ER^+ status								
No	29	27	1	ref.	-			
Yes	2	1	5.859	0.680-50.449	0.108			
$HER2^+$ status								
No	27	24	1	ref.	-			
Yes	4	4	0.633	0.214-1.871	0.408			
Ki-67	-	-	0.994	0.976-1.013	0.534			
Primary tumour size	-	-	0.999	0.988-1.011	0.904			
Lymph nodes involved								
No	19	16	1	ref.	-			
Yes	12	12	0.656	0.293-1.468	0.305			
Primary diagnosis								
Local	24	21	1	ref.	-	1	ref.	-
Metastatic	7	7	0.278	0.099-0.779	0.015[a]	0.277	0.085-0.907	0.034[a]
Palliative systemic treatment								
No	9	9	1	ref.	-	1	ref.	-
Yes	20	18	0.172	0.069-0.428	<0.001[a]	0.236	0.087-0.638	0.004[a]
First-line systemic therapy								
Combination	8	6	1	ref.	-			
Monotherapy	12	12	0.439	0.143-1.344	0.149			

[a]Statistically significant (P<0.05). CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ref., reference.

demonstrated in >50% of the population; however, looking at additional factors (such as the % local lymph node positivity), the cohort presentation was more reminiscent of NST-like BC (33).

The majority of the patients in the present study were diagnosed with squamous component, commonly with accompanying NST BC (Table I). The data did not reveal any prognostic significance associated with the histologic subtype of BC-Mp, aligning with findings reported by certain researchers (18,19) but in contrary to results published by others (34,35). Emerging data indicate that the expression of proteins serving as potential targets for novel therapies is associated with histological subtypes (36). Therefore, this factor warrants re-evaluation in the context of clinical trials or cohort studies of patients treated recently.

A total of >60% of patients in the present study presented with lung metastases, which aligns with data from other studies (18,25,37,38). In all cases, lung metastases were simultaneously the initial site of distant metastatic disease. Thapa *et al* (25) identified metastases to the lungs as a poor prognostic factor. A total of 87% of all the patients in the present study had visceral metastases confirmed at a point in the course of their disease (data not shown), contributing to unfavourable outcomes.

Table V. Literature regarding patients with metastatic metaplastic breast cancer receiving palliative systemic treatment.

First author/s, year	Participants	Recruitment period	IHC	Pathology	Systemic palliative treatment (including data about regimen type)	Outcomes	Conclusions	(Refs.)
Esbah *et al*, 2012	6	2005-2011	ER^-, 83.3%; PrR^-, 83.3%; and $HER2^-$, 83.3%	Adenosquamous carcinoma, n=2; Squamous cell carcinoma, n=2; and carcinosarcoma, n=2	CTH, n=5; CED →PE', n=1; DX, n=2; PG, n=1; PE', n=1; no data, n=1	PD, n=4; SD, n=1; and died of disease, n=4	The study proposed adding platinum to the treatment for squamous and triple negative subgroups. In the sarcoma subgroup, high dose anthracyclines could be used. The study presented data for both radically- and palliatively-treated patients.	(59)
Kim *et al*, 2021	5	Unknown	ER^-, 80%; PrR^-, 100%; and $HER2^-$, 100%	Squamous cell carcinoma, n=2; mixed metaplastic squamous carcinoma and pleomorphic invasive lobular carcinoma, n=1; and metaplastic carcinoma with heterologous mesenchymal differentiation (chondroid), n=2	Pembrolizumab + X → RTH; pembrolizumab + X → eribulin → G → P → T → sacituzumab govitecan; RTH → fulvestrant + Palbociclib → exemestane + everolimus → nivolumab + bicalutamide → nivolumab in monotherapy; pembrolizumab + X; and pembrolizumab + T → RTH → D + bevacizumab + everolimus	PR, n=2; PD, n=2; CR, n=1; and PFS, 5.3-8.0 months	Response to immunotherapy in BC-Mp can be achieved in patients with modest PD-L1 (CPS 1-10) expression. Palliative patients only.	(30)
Rayson *et al*, 1999	14	1976-1997	ER^-, 70%; PR^-, 70%; HER2 status, no data; and unknown, 15%	Spindle, n=8; squamous, n=1; osseous, n=1; chondroid, n=1; mixed BC-Mp, n=5; and unknown, n=11	14 patients with metastatic disease: CTH, n=7 including: A, n=4; CF + prednisone, n=2; P, n=2; MMC, n=2; CAF, n=1; C, n=1; CMF, n=1; M, n=1; Taxol, n=1; F, n=1; actinomycin, n=1; vincristine, n=1; tamoxifen, n=4; surgery, n=3; RTH, n=6; no treatment, n=3	PR, n=1 (A); PD, n=10; CR, n=2; SD, n=1; mOS after detection of metastasis, 8 months	Among the chemotherapeutic agents used in this cohort, none reliably produced responses in metastatic disease. The study presented data for both radically- and palliatively-treated patients.	(41)

Table V. Continued.

First author/s, year	Participants	Recruitment period	IHC	Pathology	Systemic palliative treatment (including data about regimen type)	Outcomes	Conclusions	(Refs.)
Takala *et al*, 2019	28	2002-2016	ER^-, 88%; PrR^-, 97%; and $HER2^-$, 96%	Low-grade adenosquamous, n=2; squamous, n=20; spindle, n=17; chondroid differentiation, n=11; osseous differentiation, n=2; mixed BC-Mp, n=9; and mixed type, n=17	14/28 patients with metastatic disease received palliative systemic therapy and 1 patient received palliative endocrinetherapy. First-line: D/T, n=6; X, n=2; PX, n=1; PN', n=1; DG, n=1; vincristine + MF, n=1; FEC, n=1; and D + P, n=1. Second-line: FEC, n=5; TC', n=2; C'G, n=1; and D/T, n=1. Third-line: TC', n=1; D, n=1; GP, n=1; X, n=1; and AC, n=1. Fourth-line: XN', n=2 and D, n=1. Fifth-line: FEC, n=1. Sixth-line: C'G, n=1. Seventh-line: weekly A, n=1	PR, n=2; PD, n=22; NE, n=4; SD, n=6; mOS, 3.4 months or 6.4 months if treatment was administered; mOS, 1.1 month if treatment was not administered	The response to palliative systemic therapy in metastatic BC-Mp was poor. The few responses observed in the study were in those treated with anthracyclines (FEC-regimen) and capecitabine. The study presented data for both radically- and palliatively-treated patients.	(38)
Chen *et al*, 2011	18	1988-2009	ER^-, 89.1%; PrR^-,78.2%; and $HER2^-$, 95.7%	Spindle cell carcinoma, n=8; squamous cell carcinoma, n=12; chondrosarcoma, n=1; chondromyxoid, n=1; sarcomatous, n=5; mixed, n=18; and unknown, n=1	18 patients developed metastatic disease, of which 12 received CTH. First-line: N'P, n=1; oral CE', n=1; CEF, n=1; N'FL, n=1; imatinib, n=1; T + FL, n=1; CMF, n=2; oral uracil-tegafur, n=1; EC, n=1; N'X, n=1; HT, n=1. Second-line: uracil-tegafur/P, n=1; bevacizumab + MMC, n=1; bevacizumab + IE, n=1; HN'+ FL, CEF, n=1; D+P, n=1; T + FL, n=1; HT + FL, n=1. Third-line: Cetuximab, n=1; bevacizumab + M' + MMC, n=1; CE, n=2; M' + PN', n=1. Fourth-line: H, n=1; G, n=1; TGH, n=1; N'P, n=1. Fifth-line: X/lapatinib, n=1. Sixth-line: TGH, n=1. Seventh-line: Oral E'M, n=1. Eighth-line: DH, n=1. Ninth-line: DPH, n=1. Tenth-line: EH, n=1. Eleventh-line: Oral C, n=1. Twelfth-line: VMH, n=1. Thirteenth-line: V, n=1. Fourteenth-line: H + CMF, n=1	PR, n=2. First patient: paclitaxel and 24-h high-dose fluorouracil/ leucovorin treatment. Second patient: oral uracil-tegafur for 8 months before disease progression. PD, n=10. Median time from diagnosis of metastatic disease to death, 10.65 months if palliative CTH was administered and 5.29 months if palliative CTH was not administered. mTTP of first-line chemotherapy for metastatic BC-Mp treated using taxane-based regimen was 1.55 months and non-taxane-based was 0.73 months	The response of patients with BC-Mp to systemic chemotherapy was poor. Taxane- or doxorubicin-containing regimens may be the two major categories of traditional chemotherapeutic agents worth recommending. The study presented data for both radically- and palliatively-treated patients.	(42)

Table V. Continued.

First author/s, year	Participants	Recruitment period	IHC	Pathology	Systemic palliative treatment (including data about regimen type)	Outcomes	Conclusions	(Refs.)
Lee *et al*, 2012	30	January 2001-December 2009	ER^-/PrR^-, 94% and $HER2^-$, 91%	Squamous cell carcinoma, n=35; spindle cell carcinoma, n=9; chondroid differentiation, n=7; osseous differentiation, n=2; matrix-producing, n=6; squamous + spindle, n=1; adenosquamous + spindle, n=1; squamous + chrondroid + spindle, n=1; squamous + osseous, n=1; squamous + matrix-producing, n=1; chondroid + matrix-producing, n=1	30 patients developed recurrence or *de novo* stage IV disease. CTH, n=25: Anthracycline-based, 17%; taxane-based, 35%; X-containing, 30%; and other regimens, 17%. Mean number of CTH cycles=5.56 (range, 2-15)	ORR=38.9%; CBR=50%	There was no significant difference in response to preferred CTH between BC-Mp and triple-negative invasive ductal carcinoma.	(35)
Basho *et al*, 2018	59	April 2009-November 2014	ER^-, 100%; PrR^-, 100%; $HER2^-$, 98%	No data	Prior systemic therapy for metastatic disease, n=30; prior anthracycline, n=46; prior taxane n=48; prior bevacizumab, n=4; orior mTOR inhibitor, n=4; liposomal A + bevacizumab + temsirolimus, n=38; and liposomal A + bevacizumab + everolimus, n=21	ORR=19%; CBR=36%; median PFS, 4.8 months; and mOS, 10.0 months	Prior anthracycline use was an independent predictor of worse OS. Prior taxane use was an independent predictor of improved OS. Prior systemic therapy in metastatic setting was associated with worse outcomes. BC-MP may be more sensitive to mTOR inhibition due to hyperactivation of the PI3K/Akt/mTOR pathway.	(28)
Youssef *et al*, 2020	417	2004-2015	ER^-, 73%; PrR^-, 78%; $HER2^-$, 42%; and unknown, 54%	No data	Endocrine therapy, n=43; CTH, n=156; no data regarding the regimen type or response to the treatment.	mOS, 12 months if CTH was administered and 8 months if CTH was not administered	The use of chemotherapy was associated with improved survival. Palliative patients only were included in the study.	(40)

A, doxorubicin; Akt, protein kinase B; BC-Mp, metaplastic breast cancer; C, cyclophosphamide; C', carboplatin; CBR, clinical benefit rate; CPS, combined positive score; CR, complete response; CTH, chemotherapy; D, docetaxel; DFS, disease-free survival; E, epirubicin; E', etoposide; ER, estrogen receptor; F, fluorouracil; FL, high-dose fluorouracil with leucovorin; G, gemcitabine; H, trastuzumab; HER2, human epidermal growth factor receptor 2; I, ifosfamide; IHC, immunohistochemistry; M, methotrexate; M', mitoxantrone; MMC, mitomycin C; mTOR, mammalian target of rapamycin; OS, overall survival; mOS, median OS; PFS, progression-free survival; mPFS, median PFS; N', vinorelbine; NE, non-evaluable; ORR, objective response rate; P, cisplatin; PD, progressive disease; PD-L1, programmed death ligand 1; PI3K, phosphoinositide 3-kinase; PR, partial response; PrR, progesterone receptor; RTH, radiotherapy; SD, stable disease; T, paclitaxel; TNBC, triple negative breast cancer; TTP, time to progression; V, vinblastine; X, capecitabine; →, followed by.

The present study demonstrated a poor OS in the mBC-Mp population, a finding generally supported by other studies indicating several-month OS rates (Table V) (39). Although BC-Mp is commonly claimed to be chemoresistant (8,18,40), the results of the present study revealed that receiving ≥1 line of palliative treatment significantly reduced the likelihood of death at any given time, which is consistent with data from other studies (40).

Currently, there are no established protocols or recommendations for the management of mBC-Mp, to the best of our knowledge. This can be attributed to the rarity of the condition and the incomplete understanding of its natural course. In total, 64.5% of patients received first-line systemic treatment. This was lower in previously published cohorts (38,40,41) or had a comparable proportion (38,41,42). The proportion of patients who received treatment in second and later treatment lines rapidly decreased in the present study and other studies (38,42). As highlighted by Youssef *et al* (40) in a retrospective analysis of the U.S. national registry, patients with mBC-Mp underwent palliative chemotherapy more frequently when managed in academic centres. The data from the present study were compiled from patients treated in three Reference Cancer Centres and one University Hospital. A substantial proportion of patients did not undergo treatment due to a rapid disease progression associated with poor performance status and inadequate blood test results. Certain patients experienced deterioration during the diagnostic process, such as whilst awaiting biopsy appointments with the intent of assessing HER2 and ER/PrR status in metastatic sites. It appears that expedited initiation of treatment is imperative in this population whenever feasible.

Several systemic therapy regimens were administered across different lines of treatment, revealing discernible trends within the four Units in the present study. Overall, no regimen demonstrated superiority in first-line treatment, and general responses to treatment were predominantly poor, except in cases where targeted treatments were used (anti-HER2 agents in two $HER2^+$ patients in first- and second-line treatments; aromatase inhibitor in one ER^+ patient in a first-line treatment; anti-programmed cell death protein 1 monoclonal antibody within a clinical trial in a first-line treatment; and PARPi within a clinical trial in a second-line treatment). Whilst there are suggestions regarding potentially improved responses to certain agents, these conclusions are often drawn from small case series and case reports, or extrapolated from (neo)adjuvant results, including: Taxanes (42,43), capecitabine (38), anthracyclines (38) and cisplatin (13). Responses to the treatment in the cohort in the present study were 40 and 25% in first- and second-line treatments, respectively. Similar results for first-line treatments were reported by Youssef *et al* (40) In other studies, lower rates were reported (38,42).

It is suggested that the concurrent activation of numerous signalling pathways within a tumour could elucidate the lower clinical response rates observed when using single agent targeted therapeutic strategies, and combining multiple agents may offer a potential solution to surmount this therapeutic barrier (28). However, in the present study, no differences were observed between single-agent and multimodal therapies.

Pembrolizumab, when used in combination with chemotherapy, received approval from Food and Drug Administration for treating metastatic TNBC displaying positive programmed death ligand 1 (PD-L1) expression (combined positive score ≥10) as shown in the KEYNOTE-355 study (44,45). Numerous reports have emphasized the notable expression of PD-L1 in metaplastic breast carcinomas, observed in 40-50% of cases (36,46). This suggests a potential for enhanced effectiveness of immunotherapy-based treatments within this subgroup. Case reports have illustrated positive responses and clinical benefits with immunotherapy in patients diagnosed with BC-Mp (47-50). In the present study, one patient received pembrolizumab with chemotherapy within a clinical trial, achieving a PFS of 20 months (the longest in the cohort) and an OS of 21 months. Furthermore, the SWOG1609 trial has revealed notable outcomes with the combination of the cytotoxic T lymphocyte antigen 4 inhibitor ipilimumab and programmed cell death protein 1 inhibitor nivolumab in mBC-Mp (51). Nevertheless, the application of ipilimumab or nivolumab in this population is currently restricted to a clinical trial (trial registration no. NCT02834013; https://clinicaltrials.gov/).

The study by Corso *et al* (52) revealed that *breast cancer gene 1* (*BRCA1*) mutation was the most common germline pathogenic variant within BC-Mp. Interestingly, among the 15 patients with genetic alterations, no patient was reported to have a *BRCA2* mutation. In the present study, there were 3 patients with *BRCA1* mutation (15/31 tested) and one with a checkpoint kinase 2 mutation (with unknown number of tested individuals). Only one patient (reported in the database as unknown *BRCA* status) received PARPi within a clinical trial as a second-line treatment with a PFS of 25.2 weeks. Furthermore, it has been documented that 6/31 patients had a history of other malignancies treated radically in the past. These included the following: Three cases of breast cancer, all NST and ER^+, treated >5 years before the diagnosis of BC-Mp; two haematological malignancies; and one thyroid cancer. Only limited data exists about synchronous and metachronous malignancies in the BC-Mp population (53).

Patients diagnosed with mBC with a molecular profile indicating TNBC or ER^+/PrR^+ BC may undergo treatment with sacituzumab govitecan in a second or later line of treatment, according to the ASCENT or TROPICS-02 trials. This therapeutic agent is an antibody-drug conjugate featuring an irinotecan derivative attached to a monoclonal antibody that specifically targets trophoblast cell surface antigen-2 (TROP-2) (54-56). In these trials, TROP-2 expression did not exhibit predictive value within the patient populations, which was likely attributable to the consistently elevated expression levels observed. Furthermore, it has been reported that patients with mBC also exhibit heightened TROP-2 expression (36).

BC-Mp may also exhibit molecular aberrations associated with epithelial-to-mesenchymal transition, phosphoinositide 3-kinase (PI3K), nitric oxide or Wnt/β-catenin signalling (46,57,58). Several of these potential targets for personalized treatment have been evaluated in clinical trials. *PI3K catalytic subunit alpha* (*PI3KCA)* mutations and *PTEN*) loss may contribute to heightened susceptibility to mTOR) inhibitors. In a phase 1 study by Basho *et al* (28), the safety and efficacy of combining mTOR inhibitors (temsirolimus or everolimus) with vascular endothelial growth factor inhibitor bevacizumab and liposomal doxorubicin in 52 patients with

mBC-Mp was assessed (28). Genetic testing revealed 74% of tumours had a *PIK3CA* hotspot mutation. Patients with these mutations presented with an improved objective response rate (ORR). In an ongoing phase 2 study (trial registration no. NCT05660083; https://clinicaltrials.gov/) it is hypothesised that the inclusion of the PI3K inhibitor, alpelisib, in combination with a pan-nitric oxide synthase inhibitor and nab-paclitaxel may increase the ORR in patients with HER2$^-$ mBC-Mp during the first and second lines of systemic therapy. The SABINA clinical trial, a multicentre, two-cohort, non-comparative, open-label, phase II study (trial registration no. NCT05810870; https://clinicaltrials.gov/) is aimed at evaluating the safety and effectiveness of MEN1611 (an oral PI3K inhibitor), both as a standalone treatment and in combination with eribulin. The trial specifically targets patients with HER2$^-$ mBC-Mp with alterations in PIK3CA and PTEN. There are also a single report of successful applications of combined anti-angiogenic agent and immune check-point inhibitor (50).

A limitation of the present study is its retrospective design. The low incidence of the studied malignancy poses a challenge for prospective observation. Furthermore, the study acknowledges another constraint related to the size of the population. Nevertheless, it is noteworthy that the cohort of patients ranks among the largest published cohorts concerning patients with mBC-Mp, to the best of our knowledge. Secondly, receiving systemic treatment in the metastatic setting vs. not receiving it influenced OS; however, since poor performance status was not an exclusion criterion for study entry, it is possible that more advanced patients with worse performance status were the ones not receiving systemic treatment. For patients who experienced progression during follow-up, reassessment of ER/PrR, HER2 and Ki-67 was typically not performed. This implies that the data were derived from the primary tumour assessment. Given the rapid progression and the limited likelihood of acquiring ER/PrR positivity, this practice can be justified.

The data from the present study that demonstrated worse survival in patients who progressed during follow up in comparison with patients with *de novo* metastasis are interesting, but difficult to explain. One explanation may be the small patient sample size; another hypothesis may be the limitation in the available therapeutic interventions for progressing patients. The impact of secondary mutations or genetic alterations acquired during disease progression and contribution of treatment-induced resistance mechanisms in the progressing group could also serve a role.

In conclusion, the present study demonstrated the real-world multi-centre data of one of the largest populations of patients with mBC-Mp. The study underscores the challenging prognosis of mBC-Mp, with 1- and 2-year OS rates of 38.5 and 19.2%, respectively. Notably, receiving ≥1 line of palliative treatment was associated with significantly improved OS. However, other factors such as age, Ki-67, molecular subtypes, metastatic site and chemotherapy regimen did not demonstrate a significant impact on survival. A highly negative ER/PrR and HER2 status restricted the available treatment options in most of patients with mBC-Mp. The findings highlight the need for dedicated clinical trials in mBC-Mp, emphasizing the importance of tailored therapeutic strategies and continued research to enhance outcomes in this patient population.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MP, with the support of AMM, JM, AR and RPM conceived and MP, KŚ, AK, JS, AGW, AR, JD, RPM, AMM, MK, JM, MJ and MZ were involved in designing the study. MP, JWM, KŚ, AK, MK, RPM and JS performed searches within the Cancer Centre/Hospital registry system. Organizing the database and gathering patient data were undertaken by MP, KŚ, AK, MK, AR and JD, with MP handling the statistical analysis. MP, KŚ, AK and JD confirm the authenticity of all the raw data. The first draft of the manuscript was penned by MP, whilst AR and RPM contributed to specific sections. All authors were involved in revising the manuscript and have read and approved the final manuscript.

Ethics approval and consent to participate

The Maria Sklodowska-Curie National Research Institute of Oncology Branch Krakow Ethical Committee (Krakow, Poland) granted ethical approval for the present study (approval no. 3/2023). Given the retrospective nature of the study, written informed consent was not obtained from patients, in line with the decision of the Ethical Committee.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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