Editorial

Considerations of systemic treatment for matrix-producing carcinoma with curative intent

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The metaplastic tumours (MP) of the breast comprise a heterogeneous group of diseases composed of squamous cell carcinoma, spindle cell carcinoma, matrix-producing carcinoma (MPC), and with mixed metaplastic elements (1).

MPC is a poorly understood subtype of breast cancer and accounted for 0.03% of the total malignant breast tumours, according to the Annual Breast Cancer Registry by the Japanese Breast Cancer Society in 2016 (2). It has been proposed that microglandular adenosis (MA) is a precursor. An analysis of whole exome sequencing reported a molecular progression from MA to MPC (3). There are reports describing MPC associated with MA (4,5).

It generally presents with a single growing mass on the breast, often large and not followed lymph-node axillary involvement, frequently high grade, negative for hormone receptors and Her2 origin, poor response to chemotherapy, and with worse prognosis compared with more frequent breast carcinomas (1).

Kimura *et al.* reported one of the few cases in the literature where a histologically typical MPC had a remarkable response to chemotherapy. After three years of surgery, the patient remains alive and disease free. In the reported case, a 47 years old female patient received EC (epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2) administered every three weeks for a total of 4 courses, followed by 12 courses of weekly paclitaxel (80 mg/m^2) as a neoadjuvant treatment to target the T2 (3.8 cm) N0M0 on the upper outer quadrant of the right breast. Histologically it was negative for ER, PgR, and HER2, and with a Ki67 index of 90%. There was also a biopsied confirmed 0.9 cm independent invasive ductal carcinoma in the lower inner quadrant of the same breast with ER/PgR positive (values not provided), HER2 negative, and Ki67 index of 7%. The pathological analysis of the right skin-sparing mastectomy and sentinel lymph node biopsy revealed that 0.1 cm of MPC and 0.7 cm of invasive ductal carcinoma remained. The sentinel lymph node was clear of cancer. After the patient declined adjuvant capecitabine, she was started on tamoxifen (6).

Although the authors report a case with a patient performing well after three years of follow-up, it is challenging to estimate the prognosis of this subset of a MP, given the multiple subcategories and arguably in short-term observation. Previous data suggests that prognosis is associated with the primary tumour size, since axillary involvement seems to not correlate with the primary tumour (T stage) (7). Contrastingly, the molecular composition seems to be more determinant of prognosis in MPC than the extension of the matrix component, indirectly related to tumour extension. In a study using TCGA data sets, breast cancer microarrays, and xenografted-derived mRNA dataset, TCF4 and P4HA3 were associated with positive and negative prognoses (8).

In a compilation of studies with 505 cases of metaplastic

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Table 1 Series of MBC (published outcomes)

Author/year of publication	MPC/total of MBC	Neoadjuvant ChT regimen	pCR [%]	PR [%]	PD/recurrence	Overall survivor
Wong *et al.* [2021] (1)	19/44	(Doxorubicin + cyclophosphamide + taxol +/– platinum)	1 [2]	NS	NS, but 58% DFS at a median FUP of 3 y	65% at a median FUP of 3 y
Han *et al.* [2019] (12)	31/97	Doxorubicin, cyclophosphamide, and taxane	5 [17]	NS	26 (27%)	66% with 39 m of median FUP
Shimada *et al.* [2019] (13)	5/247	(Epirubicin and cyclophosphamide +/– 5-Fluorouracil) and (Docetaxel)	0	NS	NS	NS, but 3 patients (60%) died of metastatic disease within 4 y and 2 (40%) with small or node-negative tumours remained alive after 5 y
Al-Hilli *et al.* [2019] (14)	5/18	(Anthracycline + Taxane +/– platinum); (Taxane + platinum); (Taxane + Trastuzumab); (Taxane + cyclophosphamide)	2 [11]	4 [2]	At a median FUP of 28.9 m (n=8) (50%) developed local (n=1) or distant recurrences (n=7)	At median FUP of the 8 patients (50%) alive without disease was 42.2 m
Cimino-Mathews *et al.* [2016] (15)	7/45	Anthracycline + Taxane	1 [17]	NS	NS, but 5 RFS was 64% and 5 y DMFS was 75% at a median FUP of 26 m	69% with 28 m median FUP
Aydiner *et al.* [2015] (16)	18/54	Anthracycline + Taxane	0	1 [6.2]	5 (31.2%)	68% at 3 years
Nagao *et al.* [2012] (17)	4/14	(Doxorubicin, cyclophosphamide) or (epirubicin, 5-Fluorouracil, cyclophosphamide) and a taxane	0	5 [35.7]	7 (50%)	NS

MBC, metaplastic breast cancer; MPC, matrix producing carcinoma; pCR, pathological complete response; PR, partial response; PD, progression of disease; NS, non specified; FUP, follow up; y, years; m, months; RFS, relapse free survival; DMFS, distant metastasis free survival.

breast cancer published in 2006, the prognosis was overall poor, where five years OS was between 40–68% and DFS not better than 40%. On the other hand, the authors also report their cohort of 24 patients; three patients had MPC and 18 received neo/adjuvant chemotherapy. For the MPC subset, a longer OS and DFS at five years was observed, respectively 83% and 84% (7). Similar results were found in a cohort of 167 triple negative patients, where 8 were MPC. On this study, PFS and OS were respectively 75% and 70% (9). Contrastingly, in a cohort of 53 MBC that did not receive perioperative chemotherapy or hormonal therapy and 8 were MPC. Five-year DFS and OS for MPC were 100% and, alongside low-grade spindle-cell carcinoma, considerably better than the other subgroups (high-grade spindle-cell carcinoma, metaplastic carcinoma with osseocartilaginous element, and squamous cell carcinoma) (10). In another cohort of 25 patients, accounting for 18 MPC, of which 48% were TN, median OS was 4.6 years, and interestingly, 40% had second primary tumours (11). On the other hand, Han in 2019 found a positive association of overall survival with neoadjuvant chemotherapy (hazard ratio =0.397; P=0.039; 95% CI: 0.165–0.954) and with adjuvant radiotherapy (hazard ratio =0.300; P=0.041; 95% CI: 0.095–0.950). Intriguingly, the effect on recurrence-free survival was non-significant (12).

Pathological complete response (pCR) rate seems to be another inconsistent outcome amongst studies (*Table 1*). Three out of the five cohorts mentioned by Kimura *et al.* had no pCR cases, whilst the other two report similar pCR rates of around 20% (12,13,15-17). In a recently published cohort of 44 patients, where 19 had MPC, one patient

had pCR, 13 had a partial response, 2 had no response, and 2 had disease progression. In this cohort, all patients received doxorubicin, cyclophosphamide, and taxane-based neoadjuvant regiments. Finally, and most interestingly, MPC was associated with clinic-radiological response (P=0.0036) but not the other metaplastic carcinoma subtypes (1). In a cohort reported by Al-Hilli *et al.* in 2019, accounting for 18 patients, Her2 negative patients received a mix of taxane + platinum agents or cyclophosphamide, ACT +/– platinum. None of the five MPC achieved pCR, and the authors did not disclose the percentage of PR or PD (14).

Therefore, from our interpretation of the available data, it remains challenging to state if chemotherapy would be determinant for a long-term benefit in MPC. In our view, the recommendation of neoadjuvant chemotherapy could be supported in MPC tumour in which a breast-conserving surgery is planned, once the predictors for pCR are not clearly defined. Specially since there is no deep understanding of this tumour subtypes at a genomic level, which could better predict pCR rate (18,19). Nevertheless, a multidisciplinary team meeting would be appropriate to consider adjuvant chemotherapy decisions for this tumour subtype, prioritizing the patient's preferences.

However, potential biomarkers could guide decisions, such as reported by Edenfield *et al.* in 2016, who found a significant association with outcomes if *CSFIR* gene mutation is present. They also report valuable information about currently targetable mutations such as *ERBB4* and *PIK3Ca*, which were found in relatively high frequency, respectively 36% and 48%, alongside other *TP53*, 64%, in MPC (11). Similarly, in a subsequent cohort of 28 metaplastic carcinomas, 10 were MPC, 61% had *PIK3CA/PIK3R1* pathway enriched, and 64% harboured *TP53*. However, in the MPC subset, 9/10 had *TP53* mutation, and 1 had multiple mutations, including *FGFR1*, *TP53*, *MCL1*, *RB1*, *ARID1A*, *Notch1*, and 1 *PALB2* frameshift mutation (20). Currently, target treatment for most of the mutations mentioned above is available. It would be relevant to consider offering genomic testing in the palliative setting and potential consideration for suitable clinical trials.

Finally, given the common challenges in recruiting MPC patients for clinical trials, we would encourage collaborations between institutions to consider a patient-level analysis to understand potential prognostic and predictive factors better. Moreover, prospective databases would be precious and might help answer questions regarding this rare tumour subtype.

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