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Tumour Review

Therapeutic landscape of metaplastic breast cancer

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ABSTRACT

Metaplastic breast carcinomas (MPBC) are rare, aggressive and relatively chemorefractory tumors with a high unmet need. While most are "triple negative" and lack expression of estrogen, progesterone and HER2 receptors, MPBC are associated with worse outcomes compared to conventional triple negative invasive tumors. MPBCs are genetically heterogeneous and harbor somatic mutations, most frequently in *TP53*, *PIK3CA* and *PTEN*, with emerging studies suggesting a role for novel targeted therapies. These tumors have also been associated with overexpression of PD-L1 and tumor-infiltrating lymphocytes suggesting an endogenous immune response and therefore a rationale for treatment with immunotherapies. Here, we focus on therapeutic options for this difficult to treat breast cancer subtype and encourage physicians to consider targeted therapies/immunotherapies as part of ongoing clinical trials.

Introduction

Metaplastic breast carcinoma (MPBC) represents 0.2–5% of all breast cancers and is typically very aggressive, with worse clinical outcomes than triple negative invasive breast cancers (TNBC) [1,2]. It is comprised of ductal, squamous, and/or chondroid, and spindle elements, with squamous cell carcinoma being the most frequent histological subtype. The World Health Organization (WHO) further divides metaplastic breast cancer into several subgroups: low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, squamous cell carcinoma, spindle cell carcinoma, metaplastic carcinoma with mesenchymal differentiation, mixed metaplastic carcinoma, and myoepithelial carcinoma [1].

Clinical course

MPBC typically occurs in women older than 50 years, and most often presents as a rapidly growing breast mass, which accounts for the larger size of MPBC at presentation compared to invasive ductal carcinoma (IDC) [3]. On imaging, these tumors appear as ill-defined masses without specific radiological features, and can be detected using standard mammography combined with ultrasound [4]. Nearly 90% of patients with MPBC will present with localized disease, but 50% of these patients will go on to develop distant metastasis, a risk that is twice that of TNBC [2,5]. The remaining 10% of patients with MPBC present with de novo metastatic disease. Compared to other types of breast cancer, metastasis to the axillary lymph nodes is less frequent, occurring in about 15–20% of all surgical cases [4,6]. Lung-only metastases is significantly more frequent in MPBC compared with TNBC (42 versus 18% of metastatic cases) [7].

MPBC tends to have dismal outcomes that are worse than TNBC with an average overall survival (OS) of less than one year in the metastatic setting; as low as 3.4 months in one study [8–10]. The 5-year OS ranges from 54 to 69%, compared to 89% for general IDC and 73% for TNBC [5,11,12]. Characteristics that portend worse 5-year OS and progression-free survival (PFS) include tumor size greater than 5 cm, lymph node involvement, and high Ki67 [5].

Epithelial-to-Mesenchymal transition (EMT) and stem cell-like features

The aggressive clinical behavior of MPBC is attributed to EMT, which promotes invasion, migration and development of metastases. For example, EP300, a transcriptional activator of E-cadherin, was found to have low levels of expression in MPBC, leading to a more malignant phenotype and the acquisition of drug resistance [13]. Similarly, a retrospective analysis of 27 primary MPBC tumors showed that there was reduced or absent E-cadherin expression in all non-glandular metaplastic areas, and upregulation of ZEB1, an inducer of EMT, providing in situ evidence that EMT inducers are present in non-glandular MPBC [14]. This "EMT signature" correlates to poor survival outcomes and lack of pathologic complete response (pCR) to neoadjuvant chemotherapy [15]. Studies also implicate stem cell-like features as a cause for MPBC's chemotherapy-refractory nature [15,16], as shown by upregulation of the tumor stem cell marker protein aldehyde

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dehydrogenase-1 (ALDH-1) and CD44/CD24 ratios in the non-glandular components [14].

Histologic characteristics

The histologic makeup of MPBC is diverse and can include squamous, chondroid, and spindle cells with or without the presence of IDC. There is no international consensus as to the cut-offs of metaplastic components that define MPBC, although the cutoff of > 10% metaplastic elements is often used. Some authors will use cutoffs ranging from 10 to 50% metaplastic cells in a specimen, leading to inconsistency in what is defined as MPBC [1,17]. If the term MPBC is used only when ≥ 50% of the tumor has metaplastic elements, specimens with 10–49% of metaplastic makeup will be referred to as "mixed MPBC and other subtypes." [18].

One analysis of 28 metaplastic TNBC showed that all tumors with spindle cell morphology were of claudin-low subtype, which have low expression of claudins and are usually enriched in EMT and stem-cell like features [15]. Other analyses of distinct subtypes suggest that MPBC with dominant chondroid morphology is of mesenchymal-like subtype and those with dominant squamous chondroid morphology are most often basal-like subtype, with squamous metaplasia being more heterogeneous in its appearance and less easily classified into a subtype of MPBC [19]. This highlights the histologic variability even within the classification of MPBC, which, along with molecular differences, are suggested to influence outcomes in small series. For example, a retrospective case series of 53 MPBC showed that high-grade spindle cell and pure squamous cell carcinomas were significantly more likely to have distant metastatic disease than other subtypes and thereby worse outcomes [20].

While there is no pathognomonic pattern on immunohistochemistry (IHC) to diagnose MPBC, there are some characteristics that prevail. Greater than 90% of MPBC is negative for estrogen or progesterone receptors and HER2 [21]. The most common antigens positive on IHC are cytokeratins (AE1/AE3 and MNF116) (80% positive), basal cytokeratins (34βE12, CK5/6, CK14 and CK 17) (70% positive), and luminal cytokeratins (CK8/18, CK7, and CK 19) (30–60% positive). Myoepithelial markers, particularly p63, are also frequently expressed and EGFR is positive in nearly two thirds of MPBC, more common than in receptor-matched IDC [17,22].

Molecular genetic features

There are no definitive molecular signatures defining MPBC, though MPBC is known to be genetically heterogeneous, harboring multiple somatic mutations including *TP53*, *PIK3CA* and *PTEN* [23–27]. Comprehensive genomic profiling was recently reported in the largest dataset of MPBC (n = 192), which revealed a wide variety of genomic alterations with a high prevalence of *TP53* (65%) and *PIK3CA* (35%) mutations, which may represent potential therapeutic targets [26]. Exome sequencing of paired metaplastic and adjacent conventional IDC shows nearly identical somatic mutations, indicating these are genetically related and suggests that epigenetic or noncoding changes mediate the metaplastic phenotype [28].

Early studies suggest possible efficacy of therapy targeted to the molecular signature of MPBC. For example, MPBC has been shown to have an abundance of ribosomal protein L39 (RPL39) mutations, approximately 97.5% in one study [29]. This is a gain of function mutation mediated through inducible nitric oxide synthase and, although the function of RPL39 is unknown, it is hypothesized that NOS inhibitors and RNA editing modulators may offer potential targets for treatment. Reports of high levels of angiogenesis markers, such as VEGF, also point to inhibitors of this pathway as possible therapy targets [30,31,32].

Systemic treatment

Given the rarity of MPBC, no randomized controlled trials exist to compare treatment modalities or multimodal combinations specifically in MPBC patients. Like IDC, surgery, chemotherapy, and radiation remain the mainstay of treatment for MPBC, although the poor survival points to the inadequacy of current treatment options.

Localized MPBC

In localized MPBC, surgery remains the standard of care, though there is conflicting retrospective data comparing lumpectomies versus mastectomies with clinical outcomes. An analysis of Surveillance, Epidemiology, and End Results (SEER) data from 1988 to 2006 did not suggest an association of surgery type with survival [33]. Radiotherapy, however, was beneficial in multivariate analyses with 38 and 34% decreases in death from any cause and breast-related mortality, respectively [33]. An OS benefit from radiotherapy was observed in lumpectomy as well as mastectomy patients, subset analyses suggest that the benefit of post-mastectomy radiation (PMRT) is restricted to "high risk" patients with tumors larger than 5 cm in size or more than 4 metastatic axillary lymph nodes [33]. This was also observed in an analysis of non-metastatic MPBC in the National Cancer Data Base (NCDB) which included cases from 2004 to 2013 and found that PMRT was associated with OS benefits in pT3-4/N+ ($p < 0.001$), but not in pT1-2 N0 cases [34].

A more recent SEER analysis evaluating 2010–2014 data showed that among those MPBC patients who underwent surgery, mastectomy was associated with inferior 3-year OS (hazard ratio = 2.00, 95% CI 1.31–3.06), compared with breast-conserving surgery independent of stage at presentation [35].

In the NCDB study chemotherapy was independently correlated with survival for non-metastatic MPBC [34], analysis of the SEER data confirmed the survival benefit for chemotherapy in the entire MPBC cohort, although in the subset of triple negative MPBC no association was observed [7]. In general, MPBC are regarded as more

Table 1
Selected Trials for consideration of MPBC.

Trial (Clinicaltrials.gov NCT)	Treatment setting	Therapeutic agents	MPBC or TNBC
ARTEMIS (NCT02456857)	Neoadjuvant	Liposomal Doxorubicin, Bevacizumab, and Everolimus	Selected locally advanced TNBC predicted insensitive to standard chemotherapy (progressed or did not tolerate anthracycline-based NAC), based on molecular profiling/mesenchymal gene signatures
SWOG S1418 (NCT02954874)	Adjuvant	Pembrolizumab	TNBC with residual disease following (≥1 cm or positive lymph nodes)
DART Trial (NCT02834013)	Metastatic	Nivolumab and Ipilimumab	MPBC
Morpheus-TNBC (NCT03424005)	Metastatic	Multiple immunotherapy-based treatment combinations	TNBC
Several immunotherapy trials (Phase I or pilot studies)	Neoadjuvant Adjuvant Metastatic	PD-1 or PD-L1 agents	TNBC

Abbreviations: *MPBC*, metaplastic breast cancer; *NAC*, neoadjuvant chemotherapy; *PD-1*, programmed cell death protein 1; *PD-L1*, programmed death ligand 1; *TNBC*, triple negative breast cancer.

chemoresistant compared with TNBC. Little data is available regarding the efficacy of neoadjuvant regimens in MPBC (Table 1). Retrospective analyses of a study of patients treated with neoadjuvant anthracycline/taxane based regimens, suggest that patients with MPBC perform far worse than those with TNBC, with lower pCR rates of 10% (2/21 patients with sarcomatoid carcinoma) compared to 30–40% for TNBC [36]. In addition, one case reports a patient with MPBC and squamous epithelial component who achieved near pCR with a cisplatin/anthracycline-based regimen [37]. It is important to closely monitor these patients treated with neoadjuvant chemotherapy and proceed to immediate surgery if they progress [5]. Neoadjuvant clinical trials should be strongly considered (Table 1), as this would provide the unique opportunity for incorporating other treatment modalities including immunotherapies and/or targeted agents, which can potentially optimize both pCR and resection rates. In the absence of neoadjuvant trials, anthracycline-based neoadjuvant chemotherapy can be considered, as adjuvant trials including novel therapeutics such as anti-PD-1 inhibitors would then be available to patients with residual disease after standard neoadjuvant chemotherapy (NCT02954874).

Limited data exists evaluating the role of adjuvant chemotherapy, though retrospective studies have shown that MPBC derive less benefit to standard chemotherapy regimens compared to patients with IDC [9,36]. One study suggests that clinical outcomes to adjuvant treatment may in part depend on the subtype of MPBC. In 89 non-metastatic MPBC patients, all of whom had a sarcomatoid variant, those treated with cyclophosphamide, methotrexate and 5-fluorouracil had worse survival outcomes compared to those treated with an anthracycline-based regimen [36]. Interestingly, three patients treated with a sarcoma-type regimen (doxorubicin and ifosfamide) all were relapse-free after a median follow-up of 55 months, suggesting possible activity in the sarcomatoid subtype of MPBC, though the absolute benefit of the regimen is unclear and it carries a higher toxicity profile.

Metastatic MPBC

Few studies have reported metastatic MPBC patients who achieved partial, but non-durable, responses to chemotherapy (Table 2). In one study of 7 patients treated with palliative chemotherapy, only one patient achieved a partial response (PR) with doxorubicin [9]. Another study including 23 patients treated with palliative chemotherapy including anthracyclines, taxanes, capecitabine, and vinorelbine, reported PR in 22% of patients [38]. In another study of 12 patients receiving systemic chemotherapy, no responses were observed to anthracyclines, vinorelbine or cyclophosphamide, one PR was seen with taxane-based chemotherapy [39]. In a more recent cohort of 14 patients treated with palliative chemotherapy, PR was seen in 2 cases (treated with anthracycline- or capecitabine-containing regimens) [10]. Finally, one case report showed a PR with a sarcoma-like regimen using ifosfamide and etoposide in a patient with sarcomatoid features previously unresponsive to standard chemotherapy [40].

Chemotherapeutic strategies

Currently there is no standard chemotherapy regimen for metastatic MPBC patients. While histology-driven strategies may hold some promise, i.e. platinum agents in MPBC with squamous epithelial components, or doxorubicin and ifosfamide-based regimens in MPBC with sarcomatoid variants, further studies are warranted and clinical trials are strongly recommended if available (Table 1). Table 2 lists regimens with treatment responses in both neoadjuvant and metastatic MPBC. Patients should also be tested for a germline *BRCA* mutation, and if carrier of a pathogenic mutation, should be offered platinums in the neoadjuvant/adjuvant or metastatic settings. MPBC has been associated with a high incidence of *BRCA1* methylation, observed in 63% (17/27) compared to 12% in sporadic IDC (8/66) in one study [41]. In ovarian cancer, *BRCA1* hypermethylation appears to be an indicator of improved outcomes in patients undergoing chemotherapy with cisplatin [42], but it remains to be seen if MPBC are clinically responsive to DNA-disrupting agents.

Future directions

As MPBC outcomes remain poor with conventional therapies, there is an urgent need for novel therapeutic options, studies evaluating agents such as targeted and immunotherapies are discussed below.

Targeted therapies

MPBC are enriched for varying mutations depending on their distinct histologic subtypes, and heterogeneity may even exist within distinct histologic regions of a single tumor [24]. *TP53* mutations are most common, followed by mutations in *PI3K*, suggesting that therapies targeting these mutations may be effective [23,24,26]. Preliminary data show that *TP53* mutations may also be prognostic, with longer recurrence free survival (HR 0.006, $p = 0.006$) and OS (HR 0.0005, $p < 0.0001$) compared with patients whose tumor harbors mutations in the *PI3K*, *AKT*, or *mTOR* pathways [43].

Although there are no approved targeted therapies against mutant *TP53*, *TP53* mutations have been associated with increased VEGF-A levels, which may predict sensitivity to anti-VEGF agents such as bevacizumab [44,45]. For instance, in patients with advanced cancers of several tumor types, mutant *TP53* was associated with longer PFS in those treated with bevacizumab-containing regimens [46]. Interestingly, mTOR inhibitors such as temsirolimus and everolimus have also been shown to have secondary effects on angiogenesis providing the rationale for studying the combination of bevacizumab and temsirolimus/everolimus in clinical trials [47,48]. A phase I trial including 59 patients with metastatic MPBC treated with liposomal doxorubicin (D), bevacizumab (A), with either temsirolimus (T) or everolimus (E) (DAT/DAE), revealed an objective response rate (ORR) of 21%, including 4 complete responses (CR) and 7 PR. All 4 patients who achieved a CR had a mutation in the *PI3K* pathway, further supporting the use of mTOR-targeted therapies in patients with aberrations in the *PI3K/AKT/mTOR* pathway [49]. Temsirolimus has also been studied in combination with bevacizumab and other chemotherapy agents including platinums, taxanes and anthracyclines, though in 23 patients with metastatic MPBC, DAT/DT consistently outperformed the rest resulting in a CR/PR rate of 32%. Of the two patients with CR, one carried a *PI3KA* mutation and was treated with DAT. When compared to non-metaplastic TNBCs, metastatic MPBC patients treated with DAT/DAE had improved clinical outcomes including OS (10 vs. 3.7 months, $p = 0.0003$), further supporting the utility of this regimen in this particular subtype [49]. Additionally, in a clinical trial of weekly paclitaxel with buparlisib, a pan-class I PI4K inhibitor, one patient with MPBC achieved PR with an OS of 42 months, suggesting further studies with these targeted agents should be considered [50].

As aforementioned, MPBC patients should be tested for *BRCA* mutations. In addition to being more sensitive to platinum agents, patients carrying a germline mutation may also be more susceptible to Poly (ADP-ribose) polymerase inhibitors (PARPi) which were recently approved for use in metastatic HER2-negative breast cancer [51]. This, however, has not been shown to be effective in a preclinical MPBC model. In one preclinical study, mouse models of *BRCA1* deficient carcinosarcomas resembling MPBC were treated with olaparib, a PARPi, without significant response, attributed to resistance as a result of increased expression of P-glycoprotein (Pgp) drug efflux transporter [52]. Using another PARP inhibitor, which is a poor Pgp substrate, is a potential way to circumvent this resistance, though this has not been evaluated in clinical trials.

Table 2
Chemotherapy regimens associated with treatment response in MPBC.

Author, Year [Reference]	Treatment setting	# of treated patients	Regimen/Agents used including doses if available (MPBC subtype if reported)	Treatment Response	OS
Basho, 2018[49]	Metastatic	59	Liposomal doxorubicin 30 mg/m2 IV every 3 weeks; Bevacizumab 15 mg/kg IV every 3 weeks; given with Temsirolimus 10 mg IV weekly, or Everolimus 7.5 mg by mouth daily	CR (n = 4) PR (n = 7)	Median OS 10 months
Brown-Glaberman, 2010 [40]	Metastatic	1	Ifosfamide 1.8gm/m2 (later dose-reduced by 25%) + etoposide 100 mg/m2 daily × 5 days	PR (n = 1)	8.5 months after development of metastases
Chen, 2011[39]	Neoadjuvant	12	Docetaxel/cisplatin **(Spindle cell)** Weekly paclitaxel/24-hour high-dose infusional 5FU/LV **(Squamous cell)**	PR (n = 2)	NR; Range 2.0–34.4 months after development of metastatic disease
	Metastatic	12	Weekly paclitaxel/24-hour high-dose infusional 5FU/LV **(Spindle cell)** Oral uracil-tegafur **(Spindle cell/Chondroid)**	PR (n = 2)	
Hennessy, 2006[36]	Neoadjuvant	21	FAC × 4–6 cycles **(Sarcomatoid)**	pCR (n = 2) cCR (n = 1) cPR (n = 4)	5-year OS 64%
	Adjuvant	77	Doxorubicin + ifosfamide **(Sarcomatoid)**	Relapse-free (n = 3)	
Rayson, 1999[9]	Metastatic	7	Doxorubicin	PR (n = 1, duration of 4 months)	3-year OS 71%
Takala, 2019[10]	Metastatic	14	FEC **(Mixed type)** Cisplatin + Capecitabine **(Squamous cell)**	PR (n = 2)	5-year OS 52%
Takuwa, 2014[37]	Neoadjuvant	1	Docetaxel 75 mg/m2 + Cisplatin 75 mg/m2 × 4 cycles, followed by Cyclophosphamide 500 mg/m2 + Doxorubicin 50 mg/m2 + Cisplatin 50 mg/m2 × 4 cycles **(Chondroid)**	Near pCR with no recurrence after 2.5 years (n = 1)	NR
Adams 2017 [53]	Metastatic	1	Pembrolizumab 200 mg IV on d1 + Nab-paclitaxel 100 mg/m2 IV on days 1 and 8, cycles repeated every 3 weeks **(Spindle cell)**	PR (n = 1)	NR

Abbreviations: *cCR*, clinical complete response; *CR*, complete response; cPR, clinical partial response; *FAC*, 5-fluorouracil, doxorubicin, cyclophosphamide; *FEC*, 5-fluorouracil, epirubicin, cyclophosphamide; *LV*, leucovorin; *MPBC*, metaplastic breast cancer; *NR*, not reported; OS, overall survival; *pCR*, pathologic complete response; *PR*, partial response; *5FU*, 5-fluorouracil.

Immunotherapies

Based upon the recent FDA approval of the programmed death ligand-1 (PD-L1) targeting antibody atezolizumab in combination with nab-paclitaxel for metastatic PD-L1-positive TNBC, MPBC patients should be tested and offered this combination if criteria are met. Recently, frequent overexpression of PD-L1 has been demonstrated in MPBC as compared to other breast cancer subtypes (which more frequently are PD-L1-positive in immune cells). In an IHC study, tumoral PD-L1 expression defined as ≥5%, was seen in 46% (33/72) of patients with MPBC, for both hormone receptor-positive (5/84) and HER2-positive cancers (2/32), and 9% (9/102) in TNBCs [25]. Mechanisms for PD-L1 expression remain unclear, as studies do not show significant amplification of the 9p24.1 PD-L1 locus, suggesting additional processes underlying MPBC immunogenicity [26]. Additionally, these tumors have high levels of tumor-infiltrating lymphocytes (TIL) which are indicative of an endogenous anti-tumor immune response [25,26]. Overall these findings provide the rationale for therapies harnessing the immune system. Encouragingly, there is one case report of a patient with widely metastatic MPBC refractory to several lines of chemotherapy who achieved a dramatic response to pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, given in combination with nab-paclitaxel. Correlative analyses showed PD-L1 expression in 100% of MPBC cells, with an increase in TIL following pembrolizumab treatment [53]. Based on this clinical experience, the ongoing clinical trial evaluating dual anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) blockade in rare tumor types now includes a MPBC cohort (NCT02834013).

Conclusions

While chemotherapy, surgery, and radiotherapy are routinely used in MPBC based on data in conventional IDC, outcomes remain poor. Given the identification of potential targets and the rapidly developing pipeline of targeted and immunotherapeutic agents, all patients should undergo molecular and IHC testing of their tumors as well as germline testing and if appropriate, be enrolled in clinical trials to improve the outcomes for this particularly aggressive type of breast cancer (Table 1).

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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