Management and Outcomes in Metaplastic Breast Cancer

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Abstract

Metaplastic breast cancer (MBC) constitutes a rare clinical entity with special clinicopathologic, immunohistochemical, and molecular features. Resistance to systemic therapies, whether chemotherapy or hormonal therapy, is among its main characteristics, which in turn explains the poor prognosis and renders its management a challenge. Thus, the scope of the present review is to discuss the current therapeutic strategies for MBC in clinical practice and the corresponding outcomes and to suggest possible directions for future research. Potential novel targeted therapies could provide a hope for better outcomes but limited data are available owing to the rarity of MBC. As knowledge accumulates on the pathogenesis and genetic characteristics of MBC, emphasis should be given to the implementation of more targeted treatments, which will allow more efficient and individualized management of the disease.

Introduction

Breast cancer is the most frequent malignancy and the second most common cause of cancer death in women worldwide, with an incidence of 1,779,000 cases and 464,000 deaths in 2013. It can be categorized into various histologic subtypes according to the World Health Organization classification, which is based on the cells' morphology and pathologic features. One of these histologic subtypes is metaplastic breast cancer (MBC), which is a rare pathologic entity accounting for about 1% of breast carcinomas, with an age preference of approximately 61 years. At present, MBC has been diagnosed more frequently as the pathologic examination methods have evolved and its histologic features have been more clearly determined.

In general, MBC tends to confer a worse prognosis and outcomes compared with invasive ductal carcinoma (IDC) or invasive lobular carcinoma (ILC). Thus, many clinical issues come into the foreground with respect to its definition, pathogenesis, differential diagnosis, assessment of the prognosis, and its management. Furthermore, it has yet to be clarified which imaging, clinical, or immunohistochemical factors should be evaluated to define the treatment regimens that will be implemented and the anticipated outcomes, in terms of disease-free survival (DFS) and overall survival (OS). These reasons point to the need for more preclinical research and more clinical trials to formulate specific guidelines for the management of MBC.

In that context, the present review aimed to provide an overview of the heterogeneous histopathologic and molecular pathologic features of MBC and provide information regarding how these features might affect the results of treatment. Also, our review aimed to examine the current treatment regimens and their effectiveness and to compare them with those of other mammary malignancies, such as IDC. Finally, we discuss promising targeted therapies and future directions, which will hopefully enhance the results of the present therapeutic management, improving the prognosis and increasing the survival of those with MBC.

Materials and Methods

A search of published studies was conducted in the PubMed database with an end of search date of April 30, 2016 using the following algorithm: (metaplastic) AND (breast OR mammary) AND (cancer OR cancers OR carcinoma OR carcinomas OR neoplasm OR neoplasms). The reference lists of the eligible reports were manually searched for potentially relevant studies. Case report studies, reports for which access to their full texts could not be granted and the abstracts did not provide enough information, and those not written in English were excluded.
Metaplastic Breast Cancer Outcomes

Pathology and Molecular Biology

MBC, which was first described in 1973, is histologically characterized by mixed epithelial and sarcomatoid components, organized in both glandular and nonglandular patterns. The current categorization, according to the fourth edition of the World Health Organization’s classification of tumors of the breast is based on the cells’ pathologic and molecular features and includes metaplastic carcinoma of no special type, low-grade adenosquamous carcinoma, fibromatosi-like metaplastic carcinoma, spindle cell carcinoma, squamous cell carcinoma, 3 subtypes with mesenchymal differentiation (chondroid, osteous, and other types of mesenchymal differentiation), mixed metaplastic carcinoma, and myoepithelial carcinoma.

Table 1 Classification of MBC Subtypes According to WHO Classification of Tumors of the Breast, 4th Ed

<table>
<thead>
<tr>
<th>MBC Subtypes</th>
<th>Classification of Tumors of the Breast, 4th Ed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metaplastic carcinoma of no special type</td>
<td></td>
</tr>
<tr>
<td>Low-grade adenosquamous carcinoma</td>
<td></td>
</tr>
<tr>
<td>Fibromatosi-like carcinoma</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Spindle cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Metaplastic carcinoma with mesenchymal differentiation</td>
<td></td>
</tr>
<tr>
<td>Chondroid differentiation</td>
<td></td>
</tr>
<tr>
<td>Osteous differentiation</td>
<td></td>
</tr>
<tr>
<td>Other types of mesenchymal differentiation</td>
<td></td>
</tr>
<tr>
<td>Mixed metaplastic carcinoma</td>
<td></td>
</tr>
<tr>
<td>Myoepithelial carcinoma</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: WHO = World Health Organization.

Furthermore, several mutated genes tend to be present in patients with MBC and could constitute promising targets for future innovative drugs. The most characteristic of these are the onco-suppressive p53 gene, the gene coding for phosphatidylinositol-4,5-bisphosphate 3-kinase, which is usually found in TN tumors, and the phosphatase and tensin homolog (PTEN) gene. These 2 play a crucial role in regulating the mammalian target of rapamycin (mTOR) signaling pathway. Additional genes include the cyclin-dependent kinase inhibitor 2A gene and the epidermal growth factor (EGFR) gene. The latter has been correlated with the prognosis of patients with MBC, and its pathway constitutes a probable target for novel agents such as tyrosine kinase inhibitors.

Clinical Features

Clinically, MBC usually presents in women aged > 50 years as a palpable mass with noncharacteristic imaging findings on mammography, ultrasonography, and magnetic resonance imaging, because it has a heterogeneous appearance. This renders the diagnosis challenging, because it is difficult to differentiate MBC from IDC or even from a benign lesion. In general, MBC is characterized by a large size that grows rapidly and has a high potential for metastatic spread. However, MBC tends to metastasize heterogeneously rather than through the lymphatics. Thus, axillary lymph node invasion is rare, and the lung and bones are the most common sites of MBC metastasis. This might explain why patients tend to present with an advanced stage more frequently than do those with IDC or ILC.

Finally, MBC has a greater rate of recurrence compared with IDC, either regional or distant, with the most common organ the lung.

Prognostic Factors

Although knowledge is still vague for MBC, data are available concerning the clinical and immunohistochemical factors that have been shown to affect the prognosis of patients with MBC. Specifically, age at presentation of < 40 years, skin invasion, and a squamous cell component in nodal tumors have been associated with a poorer outcome. Furthermore, the type of surgery, lymph node stage, and presence of lymphovascular invasion also seem to affect the outcome, although tumor size and grade do not.

The same applies for the hormonal receptor status of MBC, which some evidence has shown does not affect the prognosis, in contrast to IDC and ILC. Nevertheless, controversial data have also been reported, including from a study that compared patients with MBC with those with TN-IDC, high-grade IDC, and high-grade ILC. That study concluded that no differences could be found in the prognosis among these different types of breast cancer (P > .2). Regarding the molecular features, EGFR expression status, Ki-67 labeling as a measure of the proliferation rate, and stem cell and EMT markers have been associated with the interval to recurrence and the OS of patients with MBC. Finally, the effect of the histologic subtype on prognosis has been studied but the results have been contradictory. Case series studying the different histologic subtypes of MBC have found differences in the OS rates (49% for carcinomatous, 68% for matrix-producing carcinoma, 64% for spindle cell, and 63% for squamous cell carcinoma of ductal origin), with 1 study suggesting that the mixed subtype confers a worse prognosis compared with that of the others. Another multicenter study has also provided data supporting that the spindle cell subtype is the most aggressive. However, evidence has also
### Table 2 - Description of Studies of the Role of Chemotherapy for Early and Locally Advanced MBC

<table>
<thead>
<tr>
<th>Case Series</th>
<th>Patients (n)</th>
<th>Treatment</th>
<th>Stage</th>
<th>5-year DFS</th>
<th>5-year OS</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beatty et al, 2006</td>
<td>17</td>
<td>AC/CT, ACT, CMF, AC, A/T, CAF/T, CA, FAC, CT</td>
<td>I-II</td>
<td>NR</td>
<td>NR</td>
<td>PD, 11.8%</td>
</tr>
<tr>
<td>Al Sayed et al, 2006</td>
<td>9</td>
<td>AC, FAC, CMF, T, CMF, A, A/T</td>
<td>II-III</td>
<td>NR</td>
<td>Median, 38.2 mo</td>
<td>CR, 100%</td>
</tr>
<tr>
<td>Hennessy et al, 2006</td>
<td>77</td>
<td>CMF, A, A/T</td>
<td>I-II</td>
<td>48%; P = .90</td>
<td>60%; P = .41</td>
<td>NR</td>
</tr>
<tr>
<td>Bae et al, 2011</td>
<td>12</td>
<td>NR</td>
<td>I-II</td>
<td>3-year DFS, 44% versus 72.5% for TN-IDC; P = .025</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Estah et al, 2012</td>
<td>9</td>
<td>CAP, CAF, CAF+T</td>
<td>II-III</td>
<td>NR</td>
<td>NR</td>
<td>PD, 45.5%</td>
</tr>
<tr>
<td>Lee et al, 2012</td>
<td>60</td>
<td>NR</td>
<td>I-II</td>
<td>46.9%; P = .194</td>
<td>56.1%; P = .067</td>
<td>NR</td>
</tr>
<tr>
<td>Guilloton et al, 2014</td>
<td>17</td>
<td>AC, AC+T, AC+H, CMF, AC+1+H, FEC+T, MAC, TC+H</td>
<td>I-II</td>
<td>76%</td>
<td>80%</td>
<td>PD, 11.8%</td>
</tr>
<tr>
<td>Nowara et al, 2014</td>
<td>18'</td>
<td>AC, FAC</td>
<td>NR</td>
<td>Median DFS, 6.5 mo</td>
<td>NR</td>
<td>SD, 33.3%</td>
</tr>
<tr>
<td>Sanguinetti et al, 2014</td>
<td>6</td>
<td>A, CMF, T</td>
<td>III</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rakha et al, 2015</td>
<td>237</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Zhang et al, 2015</td>
<td>74</td>
<td>TA, TE, ECT</td>
<td>I-II</td>
<td>64.5%; P = .445</td>
<td>76.1%; P = .237</td>
<td>NR</td>
</tr>
<tr>
<td>Cimino-Mathews et al, 2016</td>
<td>26</td>
<td>A and/or T-based, CMF</td>
<td>NR</td>
<td>DFS (CRT, no vs. yes); HR, 3.37; 95% CI, 0.84-13.5; P = .087; RFS (CRT, no vs. yes); HR, 2.73; 95% CI, 0.80-8.38; P = .079</td>
<td>OS (CRT, no vs. yes); HR, 3.67; 95% CI, 1.09-12.4; P = .038</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Abbreviations:** A = Adriamycin or doxorubicin or anthracycline; C = cyclophosphamide (Cytoxan); ChT = chemotherapy; CI = confidence interval; CR = complete response; DFS = disease-free survival; E = epirubicin; F = 5-flurouracil; H = trastuzumab (Herceptin); HR = hazard ratio; I = ifosfamide; IDC = invasive ductal carcinoma; M = methotrexate; MBC = metaplastic breast cancer; NR = not reported; OS = overall survival; P = cisplatin; PD = progressive disease; RFS = relapse-free survival; RR = response rate; T = taxane; TN = triple negative.

One patient did not receive adjuvant ChT, but the data were included in the results.

Three patients received neoadjuvant ChT, but the data were included in the results.

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been reported implying that the histologic subtype does not have a statistically significant role as a prognostic factor (5-year DFS rate, 71.8% for spindle cell, 63.4% for squamous cell carcinoma, 69.2% for mesenchymal, 66.7% for fibromatosi-like, and 66.7% for mixed; 5-year OS rate, 76.2% for spindle cell, 75.5% for squamous cell, 80.8% for mesenchymal, 100% for fibromatosi-like, and 100% for mixed). 4 1 2

### Treatment

#### Early and Locally Advanced Disease

The treatment of early and locally advanced MBC (stage I-III) includes surgery, radiation therapy (RT), chemotherapy, and hormonal therapy.

**Surgery.** The cornerstone of treatment is surgery, mainly as mastectomy, either simple or modified, because of the tumor's large size and rapid growth. However, lumpectomy and breast-conserving surgery can also be used in specific cases with wide surgical margins (>3 cm), because they provide survival benefits similar to those with mastectomy. However, the risk of local recurrence will be increased. Thus, breast-conserving surgery should always be followed by RT to reduce the risk of local recurrence and metastasis. 23 24

**Radiation Therapy.** Adjuvant RT can be used, because it has been shown to reduce the risk of local relapse and provide a survival benefit, which might be more significant after lumpectomy than after mastectomy. 23 24 A cohort study showed that adjuvant RT provided an improvement in OS (hazard ratio [HR], 0.64; 95% confidence interval [CI], 0.51-0.82; P < .001) and disease-specific survival (HR, 0.74; 95% CI, 0.56-0.96; P < .03), when the cases were not stratified. However, this improvement was present only for OS and not for disease-specific survival when the cases were stratified according to the type of surgical procedure (lumpectomy, HR, 0.51; 95% CI, 0.32-0.79; P < .01; vs. mastectomy, HR, 0.67; 95% CI, 0.49-0.90; P < .01). 26 Similar results were reported in another case series study, with indicated an improvement in OS after RT. 27 Thus, the cited studies support the use of adjuvant RT in all cases of MBC regardless of the surgical procedure performed. Despite these benefits, RT does not seem useful for patients undergoing...
Mastectomy with tumors < 5 cm or with < 4 metastatic axillary lymph nodes. Therefore, precise guidelines are needed regarding the administration of adjuvant therapy and more data are required to reach safe conclusions.23

Adjuvant and Neoadjuvant Chemotherapy. The results of studies have pointed to limited effectiveness for chemotherapy (CtT), with MBC tending to be resistant (Table 2). At present, medical oncologists have tended to implement the standard treatment regimens used for the more common types of breast cancer (IDC, ILC), because no specific guidelines are available for MBC. However, this has led to suboptimal results, which is unfortunate, considering the greater need for CtT in MBC patients compared with those with IDC (odds ratio, 1.6; P = .001),24 because patients with MBC tend to present at a more advanced stage.25 Specifically, CtT does not seem to provide a benefit to OS, regardless of its administration in a neoadjuvant or adjuvant setting, compared with other histologic subtypes of breast cancer. In neoadjuvant CtT, taxane-based regimens seem to provide better results compared with the others,26 nevertheless, the outcomes have remained poor. In a study of 100 patients with metaplastic sarcomatoid carcinoma, 21 of whom received neoadjuvant CtT, a partial response (PR) was seen in 10%, a pathologic complete response in 5%, and a clinical PR in 20%.27 Such poor results have also been reported by other studies.28-30 However, even when CtT was administered as adjuvant therapy, the results remained poor, with 7 of 9 patients who had undergone CtT relapsing.31 Also, compared with other types of breast cancer, the outcomes of CtT for patients with nodal metastasis seemed to be poorer (3-year DFS rate, 44.4% vs. 72.5% for the MBC and TN-IDC group, respectively; P = .025).32 However, regardless of these failure patterns, adjuvant CtT remains a mainstay in treatment regimens because studies have shown that it improves the prognosis of patients, especially when administered for early-stage disease (ie, excluding stage T3 and T4). A recent case series study of 45 patients with MBC showed that patients receiving adjuvant CtT had better OS compared with those who had not.33 A case series of 285 MBC patients showed that CtT seemed to improve the breast cancer-specific survival (HR, 0.305; 95% CI, 0.143-0.650; P = .002).34 Also, another study concluded that mastectomy combined with CtT provided significant improvement in OS and DFS for those with early-stage disease compared with mastectomy alone or breast-conserving surgery with or without CtT.35 Finally, in another study, adjuvant CtT resulted in a complete response in all 9 patients and pointed to increased 3-year OS for these patients compared with those who had not received CtT.36 Furthermore, because these tumors tend to be negative for HER2 receptor (92.2%),37 targeted therapies such as trastuzumab are likely to be ineffective and therefore cannot be used as a therapeutic option.38 This is another reason the information from published studies concerning these agents is insufficient.

Hormonal Therapy. The results have also been poor with hormonal therapy (Table 3), because the tumors tend to be negative for both hormone receptors, estrogen receptor and progesterone receptor, especially its basal subtype (TN in 75%-85% of cases).39 In general, approximately < 20% of the MBC cases will be positive for hormone receptors. Therefore, hormonal therapy can only rarely be used in the therapeutic regimens for patients with MBC compared with the regimens for patients with other histologic subtypes of breast cancer.36 Even in the rare cases in which hormonal therapy can be administered, the results might not be satisfying. Thus, the prognosis is worse than that for other histologic

<table>
<thead>
<tr>
<th>Case Series</th>
<th>Patients (n)</th>
<th>Drug Regimen</th>
<th>Stage</th>
<th>5-year OS</th>
<th>5-year DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hennessy et al, 2006</td>
<td>9</td>
<td>Tamoxifen</td>
<td>I-III</td>
<td>89%</td>
<td>RFS, 53%</td>
</tr>
<tr>
<td>Lee et al, 2012</td>
<td>10</td>
<td>NR</td>
<td>I-III</td>
<td>37.5%; P = .529</td>
<td>25.4%; P = .568</td>
</tr>
<tr>
<td>Song et al, 2013</td>
<td>13</td>
<td>Tamoxifen</td>
<td>I-III</td>
<td>HR, 29%; P = .126</td>
<td>HR, 34%; P = .185</td>
</tr>
</tbody>
</table>

Abbreviations: DFS = disease-free survival; HR = hazard ratio; MBC = metaplastic breast cancer; NR = not reported; OS = overall survival; RFS = relapse-free survival.

Table 3: Description of Studies of the Role of Hormonal Therapy for Early and Locally Advanced MBC

<table>
<thead>
<tr>
<th>Case Series</th>
<th>Patients (n)</th>
<th>Drug Regimen</th>
<th>Stage</th>
<th>Survival (yr)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chao et al, 1998</td>
<td>6</td>
<td>CAF, CEF, FAP, C+T+E</td>
<td>1-III</td>
<td>3</td>
<td>NR</td>
</tr>
<tr>
<td>Rayson et al, 1999</td>
<td>7</td>
<td>Multiple drug regimens</td>
<td>1-III</td>
<td>8</td>
<td>PR, 14.3%</td>
</tr>
<tr>
<td>Herneesey et al, 2006</td>
<td>26</td>
<td>NR</td>
<td>1-III</td>
<td>12</td>
<td>NR</td>
</tr>
<tr>
<td>Chen et al, 2011</td>
<td>12</td>
<td>Multiple drug regimens</td>
<td>1-III</td>
<td>12</td>
<td>PR, 16.7%</td>
</tr>
<tr>
<td>Esbahi et al, 2012</td>
<td>5</td>
<td>TEC, C+Et, CA, T+capecitabine, C+gemcitabine</td>
<td>1-III</td>
<td>12</td>
<td>PO, 83.3%</td>
</tr>
<tr>
<td>Lee et al, 2012</td>
<td>25</td>
<td>A-based, T-based, capecitabine-containing, others</td>
<td>1-III</td>
<td>12</td>
<td>NR</td>
</tr>
<tr>
<td>Song et al, 2013</td>
<td>23</td>
<td>A, P, T, capecitabine, vinorelbine</td>
<td>1-III</td>
<td>12</td>
<td>PR, 21.7%</td>
</tr>
</tbody>
</table>

Abbreviations: A = Adriamycin or doxorubicin or anthracycline; C = cyclophosphamide (Cytoxan); CBR = clinical benefit rate; E = epirubicin; Et = etoposide; F = 5-fluorouracil; M = methotrexate; MBC = metaplastic breast cancer; OS = overall survival; NR = not reported; P = cisplatin or carboplatin; PD = progressive disease; PR = partial response; SD = stable disease; T = taxane.
types of breast cancer, as most studies have suggested. In 3 studies, endocrine therapy was used, with tamoxifen as the main agent in 2 studies. Their results showed hormonal therapy was associated with better outcomes regarding OS and relapse-free survival or DFS. Nevertheless, the results were not statistically significant.

Moreover, in a cohort study comparing the prognosis of MBC patients with that of patients with IDC and ILC, the 5-year OS tended to be lower for patients with MBC (64% vs. 81.2% vs. 80.2%, respectively), regardless of the hormonal tumor status, again highlighting that MBC is biologically more aggressive.

Metastatic Disease

As previously mentioned, MBC tends to metastasize heterogeneously and more frequently than IDC; therefore, a larger number of patients will present with stage IV disease (Table 4). Apart from those with de novo stage IV disease (10%), the probability of recurrent metastatic disease is also greater (50%) compared with IDC. This has been shown in 2 studies conducted in Korea and China with 144 and 90 MBC cases, respectively, with most metastases occurring in the lungs and brain. In analogy with adjuvant ChT, palliative systemic treatment of patients with metastatic disease has also been ineffective because of the tumor’s chemoresistance. Thus, regardless of the regimen used, the disease will either remain stable or progress. Thus, patients with metastatic disease have a short life expectancy of about 8 months.

In a study of 25 patients with metastatic MBC, who were treated with anthracycline-based, taxane-based, or capecitabine-containing regimens and other regimens, the objective response rate was 38.9%, with a clinical benefit rate (CBR) of 50%. Another study of 23 patients treated with palliative therapy regimens mainly consisting of anthracyclics, carboplatin, taxanes, capecitabine, and vinorelbine reported a PR in 21.7% and stabilization of the disease in 21.7%. Finally, in a study of 12 patients who received various systemic palliative treatment regimens, a PR was observed in only 2 patients, with progressive disease in 10. These results further support the evidence that the available treatment is far from satisfactory.

Targeted Therapies

MBC is a heterogeneous disease, not only from the aspects of the clinicopathologic presentation, but also regarding the molecular and genomic characteristics (Table 5). In addition, owing to the ineffectiveness of the current therapeutic regimens, ultimately, a need exists for novel treatments. In that context, the molecular and genomic alterations of these tumors could be used as potential targets for new drugs. Thus, genomic profiling of tumors from patients with advanced-stage MBC has been conducted. Several genes that are usually mutated in MBC have been indicated. With these results, various drugs targeting these molecular alterations have been suggested as possible and potentially effective agents against MBC. They do require further investigation in future clinical trials.

### Table 5: Summary of Studies of the Role of Therapies Targeting the mTOR Pathway in MBC

<table>
<thead>
<tr>
<th>Stage</th>
<th>DFS (mo)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/PR, 42%</td>
<td>CBR, 50%</td>
<td></td>
</tr>
<tr>
<td>PR, 22%</td>
<td>SD, 33%</td>
<td></td>
</tr>
<tr>
<td>ORR, 25%</td>
<td>Antitumoral-based RR, 32%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CR = complete response; PR = partial response; RR = response rate; SD = stable disease; Tem = temsirolimus.

In a phase III clinical trial, various temsirolimus-based regimens were administered to 23 patients with metastatic MBC. Overall, they had a response rate of 25% and CBR of 33%. The anthracycline-based regimen, specifically, led to better outcomes, with a response rate of 32% and 2 complete responses. In a phase 1 study, temsirolimus combined with bevacizumab and liposomal doxorubicin was administrated to patients with various types of cancer, including breast cancer. The reasoning for this combination of drugs was the synergistic anti-angiogenic effects of bevacizumab and temsirolimus and that the reduction of hypoxia-induced factors by temsirolimus would make the tumor more sensitive to liposomal doxorubicin. The results for 12 patients with advanced-stage MBC showed a response rate of 42%, a CBR of 50%, and CR, which applied only to the patients with MBC in that study. Finally, in a study of genomic alterations in mTOR and mitogen-activated protein kinase pathways, both of which are common
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in patients with metastatic MBC, 9 patients were treated with a combination of temsirolimus, bevacizumab, and liposomal doxorubicin. This regimen resulted in a PR of 22.2% and stabilization of disease for > 4 months in 33% of the patients; the median progression-free survival was 6.2 months.19

Much work is needed concerning targeted therapies. Genomic profiling of MBC is a crucial first step in the development of new drugs, because the genomic profile can be used to unveil potential molecular targets for this tumor.16 Nevertheless, the current trend in the research of the pathogenesis and, subsequently, the prevention and treatment of breast cancer is to examine the role of cancer stem-like cells. These cells seem to have a unique role in the self-renewal process and the heterogeneity of the tumor, which in turn might be associated with drug resistance.17 Information is increasing concerning the molecular features of these cells, because they might constitute the basis for new therapeutic approaches.18 The upcoming data could also be used in combination with the exploitation of each patient’s immune system against the tumor cells (i.e., immunotherapy). At the prediagnostic level, the potential role of activated T cells and natural killer cells against breast cancer is under investigation.19,20 However, it will require considerable time and effort to create targeted drugs with efficient tumor-specific effects and improve the prognosis of patients with MBC.

Conclusion

MBC is a rare pathologic subtype of breast cancer that, compared with IDC and other types of breast cancer, portends a worse prognosis. MBC results in many challenges to oncologists regarding the diagnosis, pathogenesis, clinicopathological features, and, more importantly, its management and treatment. At present, no standard therapeutic approach is available for this histologic subtype. For localized disease, surgery remains the cornerstone of treatment and can be followed by local RT and/or chemotherapy, hormonal therapy, trastuzumab, and other types of targeted therapies. For metastatic disease, systemic therapies can be combined with palliative care and support, which remains of utmost importance to alleviate patients’ symptoms and improve their quality of life.

The lack of tumor-specific and effective drug regimens has mainly resulted from the tumor’s heterogeneity and special characteristics. This constitutes the main issue, considering the advanced stage at which MBC usually presents and renders systemic therapy of real importance in its management. Thus, not only should patients be prompted to participate in clinical trials of promising targeted therapies, but also current research should focus on novel tumor-specific drugs to improve the prognosis and increase the survival rates of patients.

Disclosure

The authors have stated that they have no conflicts of interest.

References

44. Ioannis-Georgios Tzanninis et al