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Features of aggressive breast cancer

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ABSTRACT

Background: Aggressive breast cancer is a term commonly used in literature to describe breast cancer with a poor prognosis. Identifying and understanding the factors associated with aggressiveness could be helpful to the management of patients with breast cancer. Breast cancer is a heterogeneous disease, both clinically and biologically, which may be responsible for the wide range of survival durations for patients with metastatic disease.

Aim: The goal of this study was to identify the factors most often described in association with aggressive metastatic breast cancer (MBC).

Methods: A systematic review was performed by querying PubMed from January 1, 2012 to June 1, 2014 for "metastatic breast cancer" ("aggressive" or "poor prognosis" or "high risk"). The level of evidence to support each potential prognostic factor of aggressive MBC was also reviewed.

Results: The identified factors were grouped into 3 principle categories: clinical, biological, and patient related. Because patient-related factors may not be indicative of inherent cancer aggressiveness, this review focused only on clinical and biological factors. The factors with the highest levels of evidence to support associations with survival in metastatic breast cancer were visceral metastases, number of metastatic sites, disease-free interval, presence of CTCs, triple-negative disease, and tumour grade.

Conclusion: Identification of these factors and understanding their contribution to the aggressiveness of MBC and disease progression may lead to more personalized treatment in this patient population.

Introduction

Breast cancer is the most prevalent cancer malignancy and the leading cause of cancer-related mortality in women in developed countries [1]. In 2014 in the United States, an estimated 232,670 women will be diagnosed with invasive breast cancer, and 40,000 will die from it [2]. In 2012 in Europe, there were an estimated 463,800 new breast cancer cases and 131,200 breast cancer–related deaths [3]. Approximately 5% of patients with breast cancer in the United States are diagnosed with metastatic disease at initial presentation [4]. Furthermore, a recent study found that approximately 10% of patients diagnosed with early-stage breast cancer developed metastatic disease within a mean follow-up of 5.7 years [5].

Breast cancer is a clinically and biologically heterogeneous disease, characterized by dysregulation of multiple cellular pathways [6] and different sensitivities to treatment [7–9], which may contribute to the wide range of survival durations for patients with metastatic disease. Some types of breast cancers are more aggressive than others. "Aggressive breast cancer" is not a standard term commonly used in the breast cancer literature. However, the ability to identify factors associated with aggressive breast cancer and to predict prognosis and treatment response has a considerable impact on patient management.

Studies in early-stage breast cancer have established numerous factors prognostic of efficacy outcomes, including axillary nodal status, tumour size, oestrogen receptor status, and histological grade, among others [10,11]. There have been relatively fewer reports on prognostic factors in metastatic breast cancer (MBC). This may in part be due to the inherent difficulty in separating whether a factor is a "pure" prognostic factor, a predictive factor for response to therapy, or both. However, prognostic factors could aid in selecting treatment for the individual patient and developing risk-adjusted treatment strategies.

Here we report a systematic literature review of breast cancer publications to identify potential prognostic factors of aggressive MBC and describe studies that evaluated them.

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Methods

Identifying factors

PubMed was queried from January 1, 2012 to June 1, 2014 for the following search terms: "metastatic breast cancer" ("aggressive" or "poor prognosis" or "high risk"). The abstracts of the resulting returns were reviewed for factors that were examined with respect to prognosis, and these factors were chosen for more detailed evaluation.

Evaluating factors

Once aggressive disease factors were identified, PubMed was queried for each term specifically ("breast cancer" [prognostic OR predictive] [specific factor]), with no date ranges selected to allow a more robust analysis. If these criteria returned limited results for a given factor, then the search was further relaxed. In selecting studies to describe for the evaluation of factors, preference was given to prospective, randomized data in evaluating the prognostic ability of each factor. However, in many cases, retrospective analyses were the only studies available. Discussions were prioritized to include the most relevant, statistically rigorous (prospective and multivariate analysis where possible), and recent results possible.

Results of systematic analysis

Identification of factors

The most relevant prognostic factors associated with aggressive MBC were identified based on systematic search methods described earlier. This search returned a total of 141 results (135 in English). Three categories of factors were identified: clinical, biological, and patient-related (Table 1). Patient-related factors were not examined in detail. Other factors were excluded for further analysis for the following reasons: representation in only 1 report, relevance to early-stage breast cancer only, or difficulty evaluating the factor in other reports due to lack of uniformity in its definition.

Clinical features

Site of metastasis/recurrence

Definitions of metastatic site may vary slightly from one study to the next. It may refer to simply the presence of a lesion in that site, the first distant recurrence after treatment for early-stage disease, or the dominant site of metastasis.

Visceral metastases. Visceral lesions are those confined to visceral organs, typically the liver or lung. Approximately 70% of patients enrolled in MBC trials have visceral metastases at baseline [12–14]. Multiple studies have suggested that the presence of visceral metastases is associated with worse overall survival [15–20]. A phase III trial (N = 739) in which patients with MBC were treated with doxorubicin, paclitaxel, or the combination of both demonstrated that patients with visceral-dominant metastases had worse overall survival than those with other dominant sites of metastasis [21]. Specifically, a multivariate analysis demonstrated that visceral-dominant metastases were significant, independent predictors of overall survival (hazard ratio [HR] 1.4; $P = 0.004$; Table 2). In another robust dataset, a meta-analysis (N = 1361) performed on 10 consecutive MBC trials conducted by the Hellenic Oncology Cooperative Group (HeCOG) from 1991 through 2006 found that the presence of visceral metastases significantly associated with a worse prognosis [17]. Most patients (79.5%) received taxanes as first-line treatment. Patients with visceral metastases made up 70% of the total population. The results of a Cox model that accounted for different treatments demonstrated a 44% higher risk of mortality for patients with visceral metastases vs those without (HR 1.44; 95% CI, 1.24–1.68; $P < 0.001$; Table 2).

Brain metastases. Based on case series, the incidence of clinically evident central nervous system metastases among women with

Table 1
Identification of potential prognostic factors for aggressive breast cancer.

Factor	Represented in >1 publication?	Relevance for MBC	Selected for evaluation?
Clinical			
Site of metastasis	Yes	Yes	Yes
Number of metastatic sites	Yes	Yes	Yes
DFI	Yes	Yes	Yes
Prior therapy	Yes	Yes	No – less relevant to understand disease aggressiveness
Nodal status	Yes	No	No – less relevant to MBC
Response to prior therapy	No	Yes	No – low representation
Platelet-to-lymphocyte ratio	No	Yes	No – low representation
Biological			
ER/PR status	Yes	Yes	Yes
HER2 status	Yes	Yes	Yes
TNBC	Yes	Yes	Yes
Presence of CTCs	Yes	Yes	Yes
Tumour grade/differentiation	Yes	Yes	Yes
Tumour size	Yes	Yes	Yes
Molecular subtype	Yes	Yes	No – focus will be on clinical markers (e.g., ER/PR, HER2)
Inflammation	Yes	Yes	No – no standard marker of inflammation in these reports
Ki-67	No	Yes	No – low representation
Histology (ductal vs lobular)	No	Yes	No – low representation
Concordance of receptor status between primary tumour and metastasis	No	Yes	No – low representation
Patient-related			
Age	Yes	Yes	No – less relevant to understand disease aggressiveness
Performance status	Yes	Yes	
Race	Yes	Yes	

CTCs, circulating tumour cells; DFI, disease-free interval; ER, oestrogen receptor; HER2, human epidermal growth factor receptor-2; MBC, metastatic breast cancer; PR, progesterone receptor; TNBC, triple-negative breast cancer.

Table 2
Clinical factors associated with increased risk of death in patients with MBC.

Factor	Level of evidence	N	HR (95% CI)	*P* Value
Visceral metastasis (yes vs no)				
Sledge et al. [21]	Phase III trial – MVA	738	1.4 (NR)	0.004
Dafni et al. [17]	Meta-analysis of phase II and III trials – MVA	1361	1.44 (1.24–1.68)	<0.001
Brain metastasis (yes vs no)				
Jung et al. [25]	Retrospective review of a patient series – MVA	557	1.58 (1.04–2.41)	0.033
Largillier et al. [26]	Retrospective review of a patient series – MVA	1038	15.00 (8.17–27.50)	<0.0001
Number of metastatic sites				
Fountzilas et al. [28]				
(2 vs 1)	Phase III trial – MVA	416	1.51 (1.03–2.21)	0.03
(≥3 vs 1)			2.47 (1.68–3.63)	<0.001
Pierga et al. [27]				
(2 vs 1)	Retrospective review of multiple clinical trials – MVA	1430	1.22 (1.12–1.33)	Overall 0.000001
(≥3 vs 1)			1.49 (1.25–1.77)	
DFI				
Yamamoto [33] (≥24 vs <24 months)	Phase III trial – MVA	233	2.70 (1.92–3.79)	<0.0001
Chang [19] (≥12 vs <12 months)	Retrospective review of a patient series – MVA	346	1.59 (1.14–1.67)	0.0008

DFI, disease-free interval; HR, hazard ratio; MVA, multivariate analysis; NR, not reported.

MBC is estimated to be 10%–16% [22], whereas in autopsy series, brain metastases have been found in up to 30% of patients [23]. Brain metastases occur slightly more frequently in patients with human epidermal growth factor receptor-2–positive (HER2+) breast cancer than other molecular subtypes (14% vs 2%–11% in 1 study of 3726 patients) [24]. In a retrospective review that analysed the records of >500 patients with MBC treated at a single centre, the presence of brain metastases was significantly associated with a shorter OS than the absence of brain metastases (HR 1.58; 95% CI, 1.04–2.41; $P = 0.033$; Table 2) [25]. Similar findings were observed in a separate retrospective analysis of >1000 patients [26]. The risk of mortality was 15-fold higher for patients with brain metastases, making metastasis to the brain the most powerful predictor of survival in that study (Table 2).

Number of metastatic sites

Metastatic breast cancer trials often define groups of patients based on the number of metastatic sites, generally setting thresholds between 1 and 3 [14,27–30]. Higher numbers of metastatic sites have generally indicated a worse prognosis for patients than lower numbers of metastatic sites. For example, a phase III trial (N = 416) of patients treated with paclitaxel plus carboplatin, docetaxel plus gemcitabine, or paclitaxel monotherapy (plus trastuzumab in all patients with HER2+ disease) demonstrated that the presence of >1 metastatic site (separate analyses of 2 vs 1 or ≥3 vs 1) was a significant independent predictor of survival (Table 2) [28]. The presence of multiple metastatic sites was also confirmed as a factor associated with aggressive MBC in a retrospective review of >1400 patients treated in 8 consecutive prospective trials of anthracycline-based therapy for first-line treatment at the Curie Institute. The HR for 2 sites vs 1 site was 1.22, and the HR for ≥3 sites vs 1 site was 1.49 (overall $P = 0.000001$; Table 2) [28].

Short disease-free interval

Multiple studies have shown that early recurrence is an independent predictor of survival and that disease-free interval (DFI) is one of the strongest prognostic factors reflecting the aggressiveness of advanced breast cancer [19,31–33]. Researchers often group patients based on DFI cutoffs of either 12 or 24 months [14,19,27,33,34]. A study of patients treated in a phase III trial with either tamoxifen or medroxyprogesterone acetate combined with doxorubicin and cyclophosphamide found that patients with a DFI <24 months had a better survival prognosis than those with a DFI ≥24 months (HR 2.70; 95% CI, 1.92–3.79; $P < 0.0001$; Table 2) [33]. More recently, Chang et al. demonstrated an association between short DFI (<12 months) and a worse outcome in a series of patients (N = 346) identified retrospectively from a central laboratory [19]. The risk of mortality for patients with a shorter DFI was almost 60% higher than the mortality risk of patients with a longer DFI (Table 2).

Biological features

Histological and molecular subtypes

One of the most established factors upon which to base treatment decisions is histological subtype. In general, breast cancer can be divided into one of the following 3 subtypes based on the expression of the hormone receptors (oestrogen and progesterone) and HER2: hormone receptor–positive (59%–79%), HER2-overexpressing (22%–24%), and triple-negative (13%–24%) [35–38]. Differential gene expression profiles have also been used to classify breast cancer into molecular subtypes with distinct biologies [39]. Specifically, 5 core molecular subtypes have been identified: luminal A, luminal B, HER2-enriched, basal-like, and normal-like [40]. The basal-like and HER2-enriched subtypes were associated with the poorest outcomes [40]; however, a growing number of HER2-targeted therapies has improved the prognosis of patients with HER2-enriched disease [29,41,42]. Histological and molecular subtypes show some degree of overlap. For example, the majority of luminal A and luminal B tumours are hormone receptor–positive; nuclear staining of the proliferation marker protein Ki-67 can distinguish between the 2 subtypes (<14% of cells in luminal A and ≥14% of cells in luminal B) [6,37,43]. In addition, the majority of molecularly defined HER2-enriched disease is HER2+ in the histological classification [6,37]. Lastly, most basal-like tumours are histologically triple negative [6,37]. Some might question the degree of actionable detail that a molecular approach can provide beyond classic histological subtyping based on these data. Others might point to the incomplete overlap of subtypes as a clear indication of an opportunity to improve care.

Current treatment decisions are still based largely on histological findings so we will focus on exploring the aggressiveness of these subtypes [44]. However, trial inclusion criteria typically specify patient populations based on the expression of hormone receptors and HER2; therefore, comparisons between such subtypes are not available in the context of current randomized clinical trials.

HER2. HER2+ tumours are known to possess a number of factors associated with an aggressive disease phenotype, including lymph

node positivity, worse nuclear grade, higher mitotic index, and frequent mutations in the gene *TP53* [6,35]. In a seminal study (N = 86) of patients with early-stage breast cancer, amplification of the *HER2/neu* gene was significantly associated with both time to disease relapse ($P = 0.001$) and overall survival ($P = 0.02$) in multivariate analyses [45]. Since that study, a number of HER2-targeted therapies have been introduced that have improved efficacy outcomes for patients with HER2+ MBC, including trastuzumab, lapatinib, pertuzumab, and trastuzumab emtansine [29,41,42,46]; therefore, patients with HER2+ tumours are no longer considered to have a worse prognosis than those with HER2− tumours.

Triple-negative breast cancer (TNBC). Like HER2+ tumours, triple-negative tumours are also known to have an inherently aggressive disease phenotype, including worse nuclear grade, worse histological grade, high mitotic index, high genomic instability, and mutations or loss of the genes *TP53*, *PIK3CA*, *PTEN*, *RB1*, and *BRCA1* [6,35]. A large study of >50,000 patients from 8 regional registries in California found that the 5-year survival rates for patients with TNBC vs non-TNBC were 77% vs 93%, respectively [38]. The poor prognosis of patients with TNBC was also confirmed in a large trial of patients with MBC treated with first-line chemotherapy. In that study, a multivariate analysis demonstrated a 4.3-folder higher risk of mortality for patients with TNBC vs non-TNBC (Table 3) [47]. Unlike the hormone receptor–positive and HER2+ subtypes, no targeted agents have yet been proven useful for triple-negative disease.

Circulating tumour cells (CTCs) as prognostic and predictive markers

Circulating tumour cells (CTCs) are tumour cells detectable in blood that have been released by primary tumours or metastases [48,49]. Counting and characterizing CTCs represent a relatively recent approach to prognosis and determining response to therapy [47,49–52]. Multiple prospective studies in breast cancer patients have validated the prognostic significance of baseline CTC level on survival, and most use a cutoff of 5 CTCs per 7.5 mL of blood at baseline to define prognostic groups [47,49,53].

In a randomized, prospective multicentre study on patients (N = 177) with MBC, Cristofanilli et al. found that the CTC level, as measured before a new therapy was initiated and at the first follow-up visit, was a predictor of both progression-free survival and overall survival [53]. In a multivariate analysis, a CTC count ≥5 per 7.5 mL of blood was a significant independent predictor of worse survival compared with a CTC count <5 (HR 4.26; $P < 0.001$; Table 3). A subgroup analysis of 83 patients who were treated with first-line chemotherapy confirmed the prognostic significance of ≥5 vs <5 CTCs per 7.5 mL of blood at baseline (multivariate HR 3.45; $P = 0.01$) [54]. Interestingly, the same study found that CTC level at the first follow-up visit was also predictive of progression-free and overall survival [53].

Two more-recent prospective studies have confirmed the prognostic significance of CTCs. The first was an analysis of data from 267 patients who received first-line chemotherapy (±a targeted agent, including trastuzumab or lapatinib for HER2+ disease or bevacizumab for HER2− disease), which showed a >2-fold higher probability of mortality for patients with ≥5 CTCs per 7.5 mL of blood at baseline (Table 3) [47]. The second analysis included 468 patients with MBC who were initiating a new line of systemic therapy [49]. The HR for survival in patients with ≥5 vs <5 CTCs per 7.5 mL of blood at baseline in that study was almost 5 (Table 3).

Tumour grade

Tumour grade, a measure of the differentiation and mitotic activity of tumours, is a well-accepted prognostic marker in early-stage breast cancer [44,55]. However, studies have revealed that tumour grade is also associated with survival in MBC [26,56]. A subanalysis of a phase III trial in which patients received either methotrexate plus 5-fluorouracil or docetaxel as second-line therapy demonstrated a significant association in multivariate analysis between histological grade and overall survival [57]. Ninety-six patients had evaluable immunohistochemical samples, and the HR for grade 3 vs grade 1 or 2 was 1.95 (Table 3); although the *P* value was not reported, the 95% CI did not cross 1, suggesting a significant difference. Histological grade was also a significant, independent predictor of survival in a retrospective review of >1000 women with MBC treated at a single centre (multivariate HR 1.25; 95% CI, 1.00–1.55; $P = 0.048$; Table 3) [26].

Tumour size

Although tumour size is a component of tumour stage [44], only tumour size was identified during the systematic search of potential prognostic factors associated with aggressive MBC. Like tumour grade, primary tumour size may be thought of more as a prognostic factor for early-stage disease. However, a study of 1038 patients

Table 3
Biological factors associated with increased risk of death in patients with MBC.

Factor	Level of evidence	N	HR (95% CI)	*P* value
Histological status				
HER2 (amplified vs not)				
Slamon et al. [45]	Retrospective review of a patient series – MVA	83	NR	0.02
TNBC (yes vs no)				
Pierga et al. [47]	Prospective, multicentre study – MVA	1430	4.3 (2.1–8.8)	0.0002
Presence of CTCs (≥5 vs <5 per 7.5 mL)				
Cristofanilli et al. [53]	Prospective, multicentre study – MVA	177	4.26 (NR)	<0.001
Pierga et al. [47]	Prospective, multicentre study – MVA	267	2.4 (1.1–5.4)	0.03
Wallwiener et al. [49]	Prospective, multicentre study – MVA	468	4.79 (2.95–7.79)	<0.001
Tumour grade				
Poikonen et al. [57]				
Grade 3 vs 2 or 1	Phase III trial – MVA	96	1.95 (1.16–3.27)	NR
Largillier et al. [26]				
Grade 2 or 3 vs 1	Retrospective review of a patient series – MVA	1038	1.25 (1.00–1.55)	0.048
Primary tumour size				
Largillier et al. [26]				
>20 vs ≤20 mm	Retrospective review of a patient series – MVA	1038	1.24 (1.02–1.50)	0.027

CTCs, circulating tumour cells; HER2, human epidermal growth factor receptor-2; HR, hazard ratio; MVA, multivariate analysis; NR, not reported; TNBC, triple-negative breast cancer.

with MBC treated at a single institution found tumour size (>20 mm vs ≤20 mm) to be a significant, independent factor associated with survival by multivariate analysis (HR 1.240; 95% CI, 1.02–1.50; $P = 0.027$; Table 3) [26]. Our evaluation criteria did not return any other strongly supportive evidence in the metastatic setting, and 1 recent study specifically stated that primary tumour size was not prognostic for disease recurrence in patients with nonmetastatic disease [58].

Discussion

In this literature analysis, the highest level of evidence (large clinical trial) was available to support the following factors being associated with aggressive MBC: visceral metastases, number of metastatic sites, disease-free interval, presence of CTCs, triple-negative disease, and tumour grade [17,21,28,33,47,49,53,57]. Only retrospective reviews were available to support brain metastases, HER2 positivity, and tumour size as markers of aggressive disease [25,26,29]. However, in the case of HER2 positivity, this lack of highest-level evidence is likely due to current trial designs, which understandably provide different treatments for patients with HER2+ disease and HER2− disease. Although the absence of clinical trial data for brain metastases was somewhat unexpected, the lack of data on tumour size may have been less so, as this factor is often thought of as a marker of prognosis for early-stage breast cancer.

Even though the underlying mechanisms are not always known, some of these identified factors have shown a possible contribution to rapid disease progression or resistance to treatment. Therefore, understanding prognosis and treatment options for these patient types is of particular importance in patient management.

This review focused on clinical and biological factors associated with inherent disease aggressiveness. As such, we did not discuss a handful of identified patient-related factors that are thought to be important clinically, including age, performance status, comorbidities, and race. Also beyond the scope of this review were more recently identified factors, such as genetic mutations, markers of inflammation, and receptor concordance between the primary tumour and metastatic sites.

Although in this review histological subtyping was prioritized ahead of molecular subtyping as a prognostic tool due its current clinical use, there is evidence that molecular subtypes are also related to outcomes, including survival [37,40]. Molecular analysis allows for a more nuanced examination of tumour biology than histological subtyping. The Cancer Genome Atlas Network characterized the molecular subtypes by examining gene expression profiles, somatic mutations, structural rearrangements, copy number alterations, and epigenetic events [6]. The study described variability between and within molecular subtypes; however, it was revealed that somatic mutations in just 3 genes (*TP53*, *PIK3CA*, and *GATA3*) were present in >10% of all breast cancers. In addition, a retrospective analysis (N = 437) suggested that molecular subtyping demonstrated a potential benefit over histological subtyping in identifying specific subsets of patients that may be more vs less likely to benefit from specific treatments [37]. Future prospective studies that evaluate the efficacy of specific treatments on molecularly defined subtypes may further answer the question of the added value provided by a molecular vs histological subtyping approach.

Nuclear Ki-67 is a prognostic factor in early-stage breast cancer [59]. Although it did not meet the criteria for inclusion in this systematic review, studies have suggested that a high nuclear Ki-67 level in primary tumours may also predict poorer outcomes in patients with MBC [60,61]. In one study, a significant association was observed between Ki-67 level and shorter time to progression in patients (n = 146) treated with aromatase inhibitors (HR 1.19, $P = 0.041$) [60]. A separate study of patients being treated with endocrine therapy as first-line treatment for ER-positive MBC (n = 241) characterized Ki-67 levels as low (<10%), intermediate (10%–25%), or high (>25%) and found significant associations of Ki-67 with clinical benefit rate, time to progression, and OS ($P \leq 0.001$ for each) [61]. A recent retrospective study of 210 patients with MBC demonstrated that low levels of Ki-67 in metastatic lesions (mKi-67 ≤20%) were significantly associated with longer OS (median 25 vs 17 months; HR 0.69; $P = 0.01$) [62]. More research is needed to fully elucidate the biological implications of Ki-67 for MBC treatment.

Another intriguing subject in understanding breast cancer aggressiveness is the spectrum of somatic mutations that may contribute to breast cancer pathogenesis and resistance to therapies [63]. For example, alterations in the *ESR1* gene may lead to endocrine therapy resistance in hormone receptor–positive breast cancer [64]. Such results should only be considered hypothesis-generating at this point; however, future treatment paradigms may eventually be influenced by deep genomic analysis. Each of these recently identified factors is interesting, and continued research will give ever more biological insight as to the contribution of each of these factors to disease progression.

Advances in the overall care of patients with MBC has led to improved trial designs and the possibility that analyses of prognostic factors can be accounted for in studies' statistical plans. Data from such trials will contribute to a more comprehensive understanding of each patient's unique disease phenotype and accelerate our ability to offer personalized treatment.

Conflict of interest statement

The authors declare that they have no competing interests.

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