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Factors Affecting Treatment Outcome of Metastatic Breast Cancer: Single Institution Study

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Abstract

BACKGROUND: Metastatic breast cancer (MBC) is an incurable disease.

AIM: The goal of therapy is to prolong survival and amelioration of quality of life. However, the benefit of later systemic treatment lines is not clear.

METHODS: This was a retrospective study of 345 MBC patient., assessment of progression free survival (PFS) survival with first line of treatment and second, third, fourth, fifth, and sixth lines of therapy, and analysis of different prognostic factors.

RESULTS: The median overall survival (OS) was 31.7 month. The median PFS was 8.1 versus 3 month for first line of treatment and beyond. Where median PFS1, PFS 2, PFS 3, PFS 4, PFS 5, and PFS 6 were 8.1, 5.8, 3.8, 4.8, 3.4, and 2.6, respectively. PFS of first line was significantly prolonged in hormone positive luminal subtype, bone only metastasis, age above 35, ECOG I-II, and oligometastatic (p = 0.041, 0.038, 0.023, 0.034, 0.0001, and 0.001, respectively). Post-progression survival was 23.4 months and it was significantly prolonged in hormone positive luminal subtype, bone only metastasis, age above 35, ECOG I-II and PFS more than 6 months with first line.

CONCLUSION: PFS is reduced with using more treatment lines in MBC. Patients with luminal subtype, bone only metastasis, age above 35, ECOG I-II, and PFS more than 6 months with first line may have the best benefit from later lines.

Introduction

Breast cancer is the most common cancer worldewide and one of the leading causes if mortality among women with 10.0 million cancer deaths in [1].

In Egypt, breast cancer comes in the first place regarding women malignancies by 38.8% [2].

The main goal of treatment of metastatic cancer patients is to improve overall survival (OS) by optimization of progression free survival (PFS) of different treatment lines with keeping the best quality of life possible [3].

The 5-year survival is still poor with estimated < 30% A; however, it is highly variable [4].

In retrospective study included 13,083 women, the OS varied from 18 to 55.6 months [5].

This is may be due to inherent heterogeneity in molecular subtypes, histopathological features, difference in treatment options received by each patient [6].

This is can be seen in HER 2 positive disease, where in spite of poor prognosis of HER2 positive patients, the use of anti HER2 therapies has changed the prognosis of these patients [7].

The benefit decreases from first line to subsequent lines of treatment is commonly observed. Furthermore, lack of benefit from first-line therapy is predictive factor for less probability of benefit from succeeding therapeutic lines [8].

Many prognostic factors for metastatic breast cancer (MBC) are reported in many studies as prolonged relapse-free intervals, brain metastases or visceral metastases and estrogen receptor (ER positivity, her2neu positivity oligometastatic disease, molecular subtype, and performance status [9], [10], [11], [12], [13], [14], [15].

However, it is not clear how can we estimate the benefit of these lines. Besides, the cost of multiple systemic treatment lines is high.

The aim of the study is to determine the prognostic and predictive value of PFS with first and later lines of treatment according to different tumor subtype.

Patient and Methods

Analysis of 345 MBC female patients at the department of clinical oncology and nuclear medicine (NEMROCK), at Kasr Alainy School of Medicine, Cairo

University in Egypt between 2016 till 2021. All Female patients with pathologically proven MBC *de novo* or post-treatment and eligible for systemic treatment were included in the study. Patients with missing data were excluded from the study.

The electronic medical records were queried using C50.9 codes breast cancer diagnoses from January 2016 to January 2021 clinical, pathologic, and treatment outcome data of eligible patients will be extracted. A clean coded dataset of the eligible patients was locked down and used for final formal analyses.

We used the term clinical benefit as defined as the time to progression or death of more than 6 months after starting line of treatment and the term post-progression survival (PPS) defined as the interval between progression at first line and death or last follow-up [8].

The PFS to different lines of treatment (PFS 1, PFS 2, PFS 3, and PFS 4) and the clinical benefit at 6 month was analyzed and correlated to treatment outcome.

Ethical considerations

The study has been approved by the research ethics committee of Cairo university school of medicine and the scientific research committee of Cairo university department of oncology and nuclear medicine.

Statistical analysis

Descriptive results for categorical variables will be presented by rate and odds ratio and for numerical variables by means and standard deviation or median and range. Comparative analysis between categorical variables will be performed Chi-square test, and for numerical variables by Student's t-test. The progression-free survival will be estimated using the Kaplan–Meier curve methods.

Results

Patient characteristics are shown in Table 1. The mean age was 48.7 years and the median follow-up was 26.7 month. Most patients were metastatic from the start 46.1%.The most common subtype was luminal subtypes then Her2 enriched presented in 26.4% while triple negative breast cancer (TNBC) accounted for 12.2%.

Different treatment lines are shown in Table 2. Most of the patients received chemotherapy in first (50%), second (61.1%), third (68.1%), fourth (78.4%), fifth (60%), six (66.7%), and seventh line (100%). While single hormonal treatment represented 32.9%, 24.1%, 20%, 13.7%,16%, and 33.3% in second, third, fourth, fifth, and sixth line.

Table 1: Clinicopathological characteristics of all included metastatic breast caner patients

Parameters		Percentage
Mean age at diagnosis (years)	48.7	
Histopathological Type in Biopsy		
IDC	320	92.8
IDC with medullary features	1	0.3
IDC with mucoid activity	1	0.3
ILC	18	5.2
Medullary carcinoma	1	0.3
Metastatic adenocarcinoma	1	0.3
Mixed IDC, ILC	3	0.9
Grade in Biopsy		
I	2	0.6
II	320	92.8
III	23	6.7
ER		
Negative	96	27.8
Positive	240	69.6
Not done	9	2.6
PR		
Negative	102	29.6
Positive	234	67.8
Not done	9	2.6
Her 2 neu		
Negative	244	70.7
Positive	91	26.4
Not done	9	2.6
Biological subtype		
Luminal A	179	51.9
Luminal B	24	7.0
Her2 enriched	91	26.4
TNBC	42	12.2
Not done	9	2.6
Ki 67% (mean±SD)	32.0	20.0
Type of met disease		
De novo	159	46.1
Relapse	186	53.9
Number of metastases		
1	40	11.6
2	23	6.7
3	11	3.2
4	9	2.6
5	1	0.3
More than 5	261	75.7
Bone Metastases only		
No	108	31.3
Yes	237	68.7
ECOG		
I-II	206	59.7
III-IV	139	40.3

The median PFS and clinical benefit rate of different lines is shown in Tables 3 and 4. PFS of first line was significantly prolonged in hormone positive luminal subtype, bone only metastasis, age above 35, ECOG I-II, and oligometastatic (p = 0.041, 0.038, 0.023, 0.034, 0.0001, and 0.001, respectively) Table 5.

PFS beyond first line was 6.8 months (95% confidence interval [CI] = 5.7–8.1). Hormone positive, luminal subtype, bone only metastasis, and PFS more than 6 months in first line were the significant correlated with better PFS beyond first line Table 6.

Median OS was 3.3 years with 95%CI (2.6–3.9).

PPS was 23.4 months (95%CI = 18.1–28.6) and it was significantly prolonged in hormone positive luminal subtype, bone only metastasis, age above 35, ECOG I-II and PFS more than 6 months with first line Table 7.

Table 2: Types of treatment with each line for metastatic breast cancer patients

Parameters	Count	Column n %
Metastatic line1		
Chemo	171	50.3
Chemo/Hormonal	20	5.9
Chemo/Hormonal/targeted	3	0.9
Chemo/Targeted	29	8.5
Hormonal	112	32.9
Hormonal/targeted	4	1.2
Targeted	1	0.3
Metastatic line 2		
Chemo	132	61.1
Chemo/Hormonal	12	5.6
Chemo/targeted	14	6.5
Hormonal	52	24.1
Hormonal/Targeted	5	2.3
Targeted therapy	1	0.5
Metastatic line 3		
Chemo	79	68.1
Chemo/Hormonal	4	3.4
Chemo/Targeted	10	8.6
Hormonal	20	17.2
Hormonal/Targeted	3	2.6
Metastatic line 4		
Chemo	40	78.4
Chemo/Hormonal	1	2.0
Chemo/Targeted	1	2.0
Chemo/Targeted/Hormonal	2	3.9
Hormonal	7	13.7
Metastatic line 5		
Chemo	15	60.0
Chemo/Targeted	3	12.0
Chemo/Targeted/Hormonal	2	8.0
Hormona/targeted	1	4.0
Hormonal	4	16.0
Metastatic line 6		
Chemo	8	66.7
Hormonal	4	33.3
Metastatic line 7		
Chemo	4	100.0

Discussion

MBC is an incurable disease with the main aim of treatment is to prolong the PFS thus controlling symptoms leading to better quality of life.

In the present study, the median PFS was 8.1, 5.8, 3.8, 4.8, 3.4, 2.6 for PFS1, PFS 2, PFS 3, PFS 4, PFS 5, and PFS 6, respectively.

The PFS was similar to Bonotto *et al*. 2015 which studied the PFS benefit from first line metastatic treatment to later lines and showed PFS1, PFS2, PFS3, and PFS4 were 9, 4.4, 4, and 3 months, respectively [8].

Adding to the previous data in Park *et al*. 2015 which studied the impact of second line and later lines of chemotherapy in MBC patients which revealed that the median PFS decreased with the advancing lines of chemotherapy: 7.6 months for first line (mPFS1) as compared to 5.1 months for second line (mPFS2) versus 3.6 months for third line (mPFS3) [16].

Furthermore, this coincides with a French study Cabel *et al*., 2021, showing minimal response

Table 3: Progression free survival with each treatment line for metastatic breast cancer patients

Parameters	Median	Minimum	Maximum
PFS first line in months	8.1	0.33	123.4
PFS second line in months	5.8	0.13	45.3
PFS third in months	3.8	0.03	23.7
PFS fourth line in months	4.8	0.23	30.0
PFS fifth line in months	3.4	0.23	11.1
PFS sixth line in months	2.6	0.13	9.5

Table 4: Clinical benefit according to treatment lines for metastatic breast cancer patients

Clinical benefit of first line (n = 164)	62.8%
Clinical benefit of second line (n = 73)	52.3%
	47.7%
Clinical benefit of third line (n = 15)	76.9%
	23.1%
Clinical benefit of fourth line (n = 10)	69.7%
	30.3%
Clinical benefit beyond first line (n = 84)	68.1%

outcome beyond the third line chemotherapy in patients with metastatic triple negative disease with a PFS 3 and PFS 4 of 2.3 months (95%CI [2.3–2.5]) and 2.1 months (95%CI [1.9–2.3]), respectively [17].

The results of all studies revealed that duration of PFS decreases from first line MBC. This may be explained by resistance to chemotherapy or hormonal therapy, toxicity, or intolerance to treatment from the first line to later ones.

Table 5: Factors affecting PFS with first line treatment of metastatic breast cancer

Parameters	PFS	p-value
Hormone receptor		0.041
Positive	9.1	
Negative	8.3	
Luminal subtype		0.038
Yes	9.1	
No	8.4	
Bone only metastasis		0.023
Yes	16.4	
No	12.467	
Age		0.034
<35 years	7.933	
≥35 years	12	
ECOG		0.0001
I-II	11	
III-IV	6.4	
No. of metastasis		0.001
Oligometastatic	18.867	
Polymetastatic	12.467	

In our study patients with hormone receptor positive showed a better median PFS with first line (PFS1) than hormone receptor negative (9.1 vs. 8.3 months, 95 % CI, p = 0.041). This was a little lower than Matikas *et al*., 2021, showing a PFS of 12.4 months (95% CI 10.3–14.5) in hormone receptor positive MBC. In Park *et al*. 2015 study hormone receptor positivity

Table 6: Factors affecting PFS beyond the first line of treatment of metastatic breast cancer patients

Parameters	Median			p-value
	Estimate	95% Confidence interval		
		Lower bound	Upper bound	
Hormone receptors				
Negative	4.467	3.545	5.388	0.0001
Positive	7.700	6.517	8.883	
Her 2 enriched				
No	7.233	6.438	8.028	0.369
Yes	6.200	3.189	9.211	
Biological				
Luminal A	7.467	6.152	8.781	0.028
Luminal B	5.433	5.290	5.576	
Her 2 enriched	6.200	3.189	9.211	
TNBC	6.067	2.509	9.624	
Bone Metastases only				
No	5.933	3.630	8.237	0.013
Yes	7.467	6.554	8.380	
ECOG				
I-II	7.467	6.153	8.780	0.15
III-IV	6.333	5.003	7.663	
Types of metastasis				
Denovo	7.467	5.970	8.963	0.78
Relapse	6.467	4.623	8.311	
PFS of first line				
≤6 months	3.367	2.813	3.921	0.0001
≥6 months	10.300	8.598	12.002	

Table 7: Factors affecting post progression survival for patients with metastatic breast cancer

Parameters	Median			
	Median PPS	95% Confidence interval		p-value
		Lower bound	Upper bound	
HR status				
Negative	12.167	5.626	18.707	0.007
Positive	24.233	20.831	27.636	
Biopsy Her 2 score by IHC				
Negative	25.100	18.995	31.205	0.026
Positive	13.067	7.100	19.034	
Biological				
Luminal A	28.933	16.585	41.282	0.005
Luminal B	18.033	7.905	28.162	
Her 2 enriched	13.067	7.100	19.034	
TNBC	12.167	3.115	21.218	
ECOG				
I-II (mean PPS)	72.841	61.562	84.121	0.0001
III-IV (median PPS)	12.067	7.251	16.882	
PFS of first line				
≤6 months	15.3	7.8	18.707	0.006
≥6 months	30.4	25.4	34.636	

was a predictive factor for longer PFS 1 (HR 0.57; 95% CI, 0.42–0.76; p < 0.001) [16], [18].

Furthermore, biological subtype is illustrated as a predictive factor for PFS, this is obvious in longer PFS with luminal A disease patients with median PFS beyond the first line therapy of 7.4 months versus 5.4, 6.2, and 6 months with luminal B, Her 2 enriched and TNBC, respectively (CI = 95%, p = 0.028).

In our study, patients with TNBC disease showed a median PFS in the first line of 8.4 months showing no statistical significance among other subtypes with a p value 0.19. This was lower than Matikas *et al*., 2021, with a median PFS of 10.9 months in the TNBC group (95% CI 9.8–12.1) [18].

PFS of first line of more than 6 months is significantly associated with better PFS beyond first line and PPS. This is similar to results of many studies as the results of park *et al*., Cabel *et al*., 2021 which revealed that PFS after first-and second-line chemotherapy was correlated with OS and PFS with later lines [16], [17].

It was noted in our study that PPS showed a median 23.4 (95% CI 18.2–28.7) months. It was noted that PPS was affected by some factors as hormone receptor, Her 2 status, biological subtype, performance status, and PFS with first line more than 6 months. In Bonotto *et al*. 2015, the median PPS was 18.3 months and it was correlated with visceral localization, HER2neu status, and PS at first line [8].

The study was limited by being retrospective with limited number of patients and short follow-up. Novel Target and hormonal drugs were not available at the time of the study. This may have decrease the PFS and OS of MBC in the study population.

Conclusion

PFS is declining with more treatment lines in MBC. PFS of first line was significantly prolonged in hormone positive luminal subtype, bone only metastasis, age above 35, ECOG I-II. and oligometastatic.

Patients with luminal subtype, bone only metastasis, age above 35, ECOG I-II, and PFS more than 6 months with first line may have the best benefit from later lines.

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