Impact of Different Lines of Palliative Chemotherapy in Patients with Metastatic Breast Cancer

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Abstract

Back ground and objectives: Metastatic breast cancer (MBC) is a heterogeneous disease that exhibits different clinical scenarios, ranging from solitary metastatic lesions to multiple organ involvements. No gold standard treatment exists for MBC and no specific guidelines are available. Although, the improvement in overall survival (OS) observed in the last decades mainly related to the contributions of various therapies, metastatic disease remains the primary cause of death in the majority of patients with breast cancer. This study aims to determine the benefit of different lines of chemotherapy in patients with MBC and to identify patients who have better benefit from the treatment.

Methods: We conducted a retrospective study of 182 MBC patients who received palliative chemotherapy at medical oncology department of South Egypt Cancer Institute (SECI), Assuit University between January, 2012 and December, 2017. A total of 182, 130, 72 and 29 patients received first-, second-, third-, and fourth-line chemotherapy, respectively. Chemotherapy groups were defined according to the principle agents used: anthracycline-, taxane-, capecitabine-, platinum-based and others.

Results: The median progression free survival (mPFS) decreased with the advancing lines of chemotherapy: it was 5 ms for first line versus 4 ms for second line versus 3 ms for third line and 3 ms for fourth line. In addition, we found that OS was significantly correlated with response rate and mPFS of first line of chemotherapy. OS when mPFS of the first line >5 ms was 19 (16.3-21.69) while it was 14 (11.4-16.6) when mPFS ≤ 5 ms p=.008. In addition both CR and RD after first line of chemotherapy were significantly related to longer OS as it was 17 (0-45.8) and 23 (17.08-28.91) respectively P= .016.

Conclusion: Both of overall response rate (ORR) and mPFS decrease with the advancing lines of chemotherapy. In addition, the response rate and mPFS of the first-line therapy are important prognostic factors for OS.

Keywords: metastatic breast cancer, survival, overall response rate.

Introduction:

Breast cancer is the most frequently diagnosed cancer in the vast majority of countries and is also the leading cause of cancer death over 100 countries [1]. Worldwide, among females there were about 2 261 419 newly diagnosed breast cancer cases which represented (24.5%) of newly diagnosed cancer cases in 2020 [2].

In Egypt, among females breast cancer represent 38.8% of all cancer cases ,with proportion highest in upper Egypt (38.72%), next in lower Egypt (33.22%), lowest in middle Egypt (26.84%) [3].

About 6–10% of breast cancer patients still present with distant metastasis (DM) and 30% with regional lymph node metastasis [4]. In addition, an estimated 20–50% of women diagnosed with early stage breast cancer will eventually develop metastatic disease [5]

Regardless of age, the goals of treatment for MBC are to control the cancer as best as possible, while maintaining the highest functional level and QOL as possible. Life expectancy, comorbidity, drug interactions and functional status should be considered when making treatment decisions in the setting of metastatic cancer [6].

Although first-line regimens have shown improved survival and QOL in various randomized trials, few studies have showed efficacy of chemotherapy beyond first-line agents. Excluding hormonal therapy, anthracycline- and taxane- containing regimens are considered the first-line chemotherapy agents for human epidermal growth factor 2 (HER2) negative MBC [7].

After tumors progress on these first line regimens, other chemotherapeutic agents can be used, including capecitabine, cisplatin, gemcitabine and vinorelbine. Although these drugs have been used as second or third line treatment, survival gain and preservation of QOL remain debatable [8]. Therefore, future studies to detect the benefit of chemotherapy beyond first-line treatment have become necessary, with the introduction of these more effective chemotherapeutic drugs for the treatment of MBC [9].

Patients and Methods:

Patients:

We conducted a retrospective study of 182 patients who received palliative chemotherapy for MBC at medical oncology department of SECI, Assiut

University between January, 2012 and December, 2017. The study was conducted in accordance with the protocol approved by Ethical Committee rules at SECI.

Clinical data, such as age, performance status and the presence of visceral involvement, were collected at the initiation of the first-line chemotherapy for MBC patients. In addition, data on hormonal receptor (HR) and HER2 status and types of adjuvant systemic treatment were collected for all patients from their medical records. In the present study, we defined HR positive disease as > 1% of tumor cells with estrogen receptor (ER) or progesterone receptor (PR) expression on immunohistochemical analysis. The Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0, was used to assess the efficacy for measurable lesions using the clinical or radiologic findings [10].

Oligometastatic breast cancer was defined as MBC with single or few detectable metastasis less than or equal to three in one site. Progression free survival (PFS) of patients receiving each drug defined as the interval from the date of the first administration of the specific drugs to the date of the first documented tumor progression or death from any cause. OS defined as the interval from the diagnosis of breast cancer to death from any cause or the last follow-up date. Disease free interval (DFI) defined as the interval between surgery and the date of diagnosis of the first distant relapse. ORR defined as sum of rates of complete response (CR) and regressive disease (RD). Patients with an initial diagnosis of metastatic disease were defined as synchronous MBC, others who developed DM after receiving adjuvant treatment were defined as metachronous MBC.

Treatment:

Five groups of chemotherapy were defined according to the principle agents used: anthracycline-, taxane-, capecitabine-, platinum-based, and other drugs. The patients who received combination regimens such as a taxane plus platinum agent were assigned to taxane group, and liposomal anthracycline was the anthracycline based chemotherapy used as third or fourth line.

Statistical analysis:

All statistical analyses were performed using IBM SPSS Statistics version 20 (SPSS Inc., Chicago, IL, USA). Categorical data were presented by frequencies and percentages, while Chi-square tests were used for comparisons between groups. Continuous data were reported as means ± standard deviations and\or median and range (min - max), Kaplan-Mayer survival curve and log-rank test were performed for comparison between PFS of drug regimens of each line of therapy. Cox regression analysis were performed to detect hazard ratio of clinical factors for OS. In all statistical tests p-value <0.05 was considered statistically significant.

Results:

Among the 182 patients, with a median age of 50 years (range 28-74 years). Eighty-one patients (44.5%) were HR positive MBC, thirty-five patients (19.2%) were HER2 positive, and twenty-one patients (11.5%) were triple negative breast cancer (TNBC). Eighty-seven (47.8%) patients were initially diagnosed as synchronous MBC, while ninety-five (52.2%) patients were metachronous MBC, Patient characteristics are listed in table (1).

Table (1): Patients characteristics (n=182)

Variables	Freq. (%)
Age (Years)	
≤ 45	69 (37.9%)
>45	113 (62.1%)
Median (Range)	50 (28-74)
Type of patients	
Synchronous	87 (47.8%)
Metachronous	95 (52.2%)
Pathology	
IDC	163 (89.6%)
ILC	11 (6.0%)
Mixed lobular & IDC	3 (1.6%)
Metaplastic carcinoma	3 (1.6%)
Undifferentiated	1 (0.5%)
Phylloids tumor	1 (0.5%)
Tumor grade	
Grade 2	153 (84.1%)
Grade 3	29 (15.9%)
ER&/or PR (29 missing)	
Positive	81 (44.5%)
Negative	72 (37.6%)
HER2 neu (88 missing)	
Positive	35 (19.2%)
Negative	59 (32.4%)
Triple negative	21 (11.5%)
Metastasis number	
Oligometastasis	79 (43.4%)
Polymetastasis	103 (56.6%)
Type of metastasis	
Bone only	14 (7.7%)
Visceral (lung + liver)	54 (29.7%)
Brain only	3 (1.6%)
Skin & lymph nodes	24 (13.2%)
Multiple	87 (47.8%)
Visceral crisis	121 (66.5%)

Data presented as mean ± SD , Median (min – max) or number & percentage n(%).
ER = estrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor

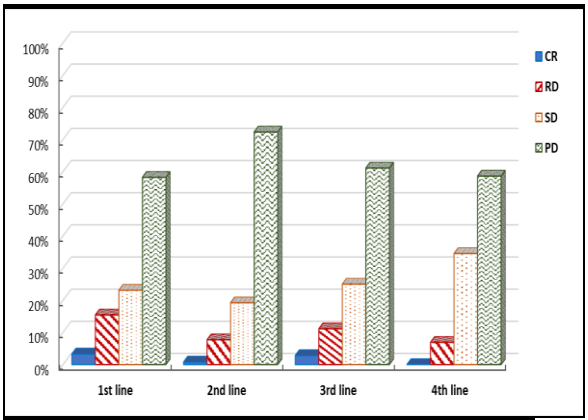
A total of 182, 130, 72 and 29 patients received first-, second-, third-, and fourth-line chemotherapy, respectively. A total of 80 patients (44.0%) received anthracycline based chemotherapy as first-line therapy, Fifty-three patients (40.8%) received taxane based regimens as second-line therapy, and both taxane based and platinum based were given at equal frequency 19 patients (26.4%) as third-line chemotherapy, while 15 patients (51.7%) received platinum based chemotherapy as fourth-line chemotherapy, as shown in table (2).

Table (2): Different types of chemotherapy in different lines of treatment

Regimens	First line	Second line	Third line	Fourth line
Anthracycline based	80 (44.0%)	10 (7.7%)	8 (11.1%)	4 (13.8%)
Taxane based	57 (31.3%)	53 (40.8%)	19 (26.4%)	4 (13.8%)
Capecitabine based	25 (13.7%)	40 (30.8%)	18 (25.0%)	5 (17.2%)
Platinum based	13 (7.1%)	15 (11.5%)	19 (26.4%)	15 (51.7%)
Others	7 (3.8%)	12 (9.2%)	8 (11.1%)	1 (3.4%)

The mPFS decreased with the advancing lines of chemotherapy: 5 ms for first line (mPFS1) versus 4 ms for second line (mPFS2) versus 3 ms for third line (mPFS3) and 3 ms for fourth line (mPFS4).

Although the ORR to chemotherapy decreased with the increasing number of lines, the response rate was different in the same lines, depending on the chemotherapeutic regimen. As first-line therapy, anthracycline-based chemotherapy showed the highest ORR (23.8%). For second-line therapy, a capecitabine-based regimen yielded the highest ORR (12.5%), platinum-based chemotherapy resulted in highest ORR for third- and fourth-line therapies, (31.6%) and (13.3%) respectively and are shown in table (3). Difference in responses of chemotherapy according to lines of therapy are shown in figure (1).



CR	6 (3.3%)	1 (0.8%)	2 (2.8%)	0
RD	28 (15.4%)	10 (7.7%)	8 (11.1%)	2 (6.9%)
SD	42 (23.1%)	25 (19.2%)	18 (25.0%)	10 (34.5%)
PD	106(58.2%)	94 (72.3%)	44 (61.1%)	17 (58.6%)

Figure (1): Difference in the response of chemotherapy according to the line of therapy

Prognostic factors associated with OS were analyzed, In univariate analysis adjuvant chemotherapy was significantly associated with OS (HR 0.72;CI 0.54 – 0.97 ; P 0.031), also mPFS of first line chemotherapy was significantly associated with OS, less than or equal to the median (≤5ms) vs more than the median (>5ms) (HR1.52 ; CI ,1.12 – 2.04 ; P 0.006). In multivariate analysis, adjuvant chemotherapy & mPFS of first line chemotherapy (≤5ms vs >5ms) were still significantly associated with OS (HR 0.22;CI 0.05 – 0.89; P 0.035),(HR 2.06;CI 1.25 – 3.39; P 0.005) respectively, also, HER2 negativity was significantly associated with better OS (HR 0.54 ;CI,0.29 – 0.98 ;P 0.045) as shown in table (4).

The median OS among studied patients was 17 ms (95% CI, 14.8 -19.2 ms). There was difference in median OS in synchronous (21 ms; 95% CI, 17.9 – 24.0) vs metachronous (16 ms; 95% CI 14.1 – 17.9) MBC but not statistically significant as shown in figure (2).

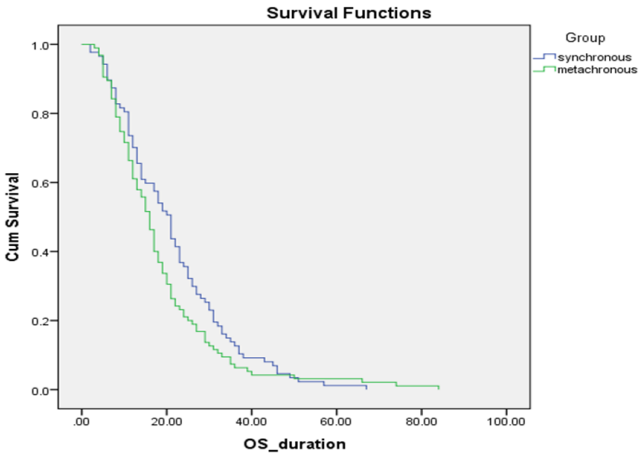


Figure (2): Overall survival in studied groups

OS was significantly related to difference in mPFS and response to first line of chemotherapy. OS when mPFS of the first line >5 ms 19(16.3-21.69) was significantly longer compared to OS when mPFS of the first line ≤ 5 14(11.4-16.6) p=.008. In addition, both CR and RD after the first line of chemotherapy were significantly related to longer OS as it was 17(0-45.8) and 23 (17.08-28.91) respectively P= .016 as shown in table (5).

Table (3): Clinical Efficacy of chemotherapeutic regimens in each line of therapy

Regimen	First Line (n = 182) (mPFS1= 5 mo ; 95% CI = 4.5-5.5)		Second Line (n =130) (mPFS2 = 4 ; 95% CI =3.4 -4.6)		Third Line (n = 72) (mPFS =3 ; 95% CI=2.5 - 3.5)		Fourth line (n= 29) mPFS= 3 ; 95% CI=2.2-3.8)	
	MPFS1	**ORR1 (%)**	**MPFS2**	**ORR2 (%)**	**MPFS3**	**ORR3 (%)**	**MPFS4**	**ORR4 (%)**
Anthracycline based	5 (4.4 – 5.6)	19 (23.8%)	5 (0.87 – 9.1)	2 (20%)	3 (2.2 – 3.8)	1 (12.5%)	3 (2.2 – 3.8)	NA
Taxane based	6 (4.9 – 7.1)	13 (22.8%)	4 (3.4 – 4.6)	3 (5.7%)	4 (3.2 – 4.8)	NA	3 (2.0 – 5.9)	NA
Capecitabine based	5 (2.6 – 7.4)	1 (4.0%)	4 (2.8 – 5.2)	5 (12.5%)	3 (2.5 – 3.5)	1 (5.6%)	6 (1.7 – 10.3)	NA
Platinum based	5 (3.9 – 6.1)	1 (7.7%)	4 (2.9 – 5.1)	NA	3 (2.3 – 3.7)	6 (31.6%)	3 (2.1 – 3.9)	2 (13.3%)
Others	5 (2.4 – 7.6)	NA	5 (3.9 – 6.1)	1 (8.3%)	4 (2.7 – 5.3)	2 (25.0%)	6	NA
P value *	.222	0.085	0.399	0.344	0.690	0.042^	0.390	0.735

** Kaplan-Mayer Survival analysis and Chi-square test were used.*

Data in parentheses are 95% CIs, unless otherwise noted.

Abbreviations: CI = confidence interval; mPFS1 = median progression-free survival of first-line therapy; mPFS2 = median progression-free survival of second-line therapy; mPFS3 = median progression-free survival of third-line therapy; NA =not available; ORR = objective response rate (complete response plus partial response).

Table (4): Factors associated with overall survival of studied patients

Factors	**Univariate Analysis**		**Multivariate Analysis**	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Synchronous vs metachronous	1.27 (0.94 – 1.70)	0.116	.770 (0.21 – 2.75)	0.688
Age (≤ 45 vs. >45 yrs)	1.08 (0.79 – 1.45)	0.640	1.51 (.937 – 2.45)	0.090
DFI (>2 vs. ≤ 2 yrs)	0.83 (0.54 – 1.26)	0.378	0.682 (0.35 – 1.32)	0.259
Hormone receptors (+ vs. -)	1.30 (0.94 – 1.79)	0.106	0.60 (0.295 – 1.23)	0.167
HER-2 neu (+ vs. -)	0.88 (0.58 – 1.35)	0.561	0.54 (0.29 – 0.98)	0.045 ^
Adjuvant Chemotherapy (yes vs. no)	0.72 (0.54 – 0.97)	0.031 ^	0.22 (0.05 – 0.89)	0.035 ^
Adjuvant hormonal therapy (yes vs. no)	1.16 (0.75 – 1.77)	0.504	2.01 (0.86 – 4.70)	0.106
Visceral crisis (yes vs. no)	0.99 (0.73 – 1.36)	0.995	1.13 (0.69 – 1.85)	0.624
mPFS1 (>5 vs. ≤ 5 months)	1.52 (1.12 – 2.04)	0.006 ^	2.06 (1.25 – 3.39)	0.005 ^

^ significant p-value.

Abbreviations: HR = hazard ratio; CI = confidence interval; mPFS1 = median progression-free survival of first-line therapy; DFI = disease free interval.

Table (5): Median OS according to mPFS and response of first line chemotherapy

	Median OS 95%CI
mPFS of first line chemotherapy	
≤ 5	*14(11.4-16.6)*
>5	*19(16.3-21.69)*
P value*	*.008^*
Response of first line chemotherapy	
CR	*17(0-45.8)*
RD	*23(17.08-28.91)*
SD	*17(11.44-22.55)*
PD	*15(11.89-18.1)*
P value*	*.016^*

*Kaplan-Mayer Survival analysis was used

^ *significant p-value.*

Abbreviations: mPFS =median progression free survival; CR = complete response;; RD = regressive disease; SD = stationary disease ;PD = progressive disease.

Discussion:

A fundamental proportion of patients with breast cancer presented with metastatic disease or progress to be metastatic. MBC has multiple clinical presentations and treatment depends on multiple factors such as the patient's tumor characteristics, treatment history and performance status [11]. As anthracyclines and taxanes commonly used in the earlier stages of disease, treatment selection in the second- and later-line settings becomes more challenging as drug resistance often limits therapeutic options [12].

In our study, a total of 182, 130, 72 and 29 patients received first-, second-, third-, and fourth-line chemotherapy, respectively. Our study demonstrated that 74 % of patients received anthracycline- or taxane-based chemotherapy as first line, in accordance with the study done by park et al which reported that > 80% of patients received anthracycline- or a taxane- based as their first-line chemotherapy [9].

As regards ORR, our study demonstrated that anthracycline-based chemotherapy showed the highest response rate (23.8%) when used as first line therapy, However a capecitabine-based regimen yielded the highest response rate (12.5%) as second line, platinum-based chemotherapy resulted in highest response rate (31.6%) as a third line, on the other hand, Park et al study announced that anthracycline-based regimens showed highest response rate when used as first line, while taxane-based regimen yielded the highest response rate as second line and capecitabine-based chemotherapy achieved better response rate as a third line [9].

In our study, we found that mPFS decreased with subsequent lines of chemotherapy, first line was 5 ms (4.5-5.5), second line was 4 ms (3.4-4.6) and third line was 3 ms (2.5-3.5), and these results were close to Dufrense et al study which included 943 patients and reported that mPFS of first line was 9.3 ms, second line was 5.9 ms, third line was 4.63 ms [13], and that may be due to smaller sample size in our study.

Bernardo et al analyzed 992 women treated with chemotherapy for MBC over a 8-year period and reported that PFS ranged from 9.2 ms to 7.8 and 6.4 ms for the first, second and third-line, respectively, with no significant decrease observed beyond the third-line (median 5.2 ms, range 4.8–6.2) [14].

As regards PFS, in our study we found that PFS with taxane-based chemotherapy was longer than other chemotherapeutic agents when used as first and third lines, anthracycline-based chemotherapy associated with better PFS when used as second line chemotherapy and was not matching with results of Park et al study which reported that anthracycline-based chemotherapy yielded the longest PFS when used as first line chemotherapy, while taxane-based chemotherapy showed highest PFS as a second line chemotherapy, while PFS when capecitabine-based chemotherapy used as third line chemotherapy was the best [9].

In our study there was a significant association between mPFS and response of the first line and median OS. Median OS when mPFS of first line above than the median was longer 19(16.3-21.69) p=.008, both CR and RD were significantly associated with prolonged median OS 17(0-45.8) and 23(17.08-28.91) respectively P= .016, and these results were close to Greenberg et al study which reported that from 263 patients who achieved CR with first line chemotherapy approximately 18% remain disease-free for more than 5 years following treatment with doxorubicin and alkylating-agent-based regimens and more than 10% of them remain disease-free for periods exceeding 20 years, because of this result, one can take into account that response rate is a major touchstone to estimate the efficacy in first line [15].

As regards OS, our study presented that OS in synchronous MBC was 21 ms (95%CI ,17.9 – 24.0) longer than metachronous MBC which was 16 ms (95% CI 14.1 – 17.9) but not statistically significant, p=.105, and these results were similar to results of Lobbezoo et al study which included 815 patients and reported that median OS of patients with synchronous MBC was 29.4 ms (95% CI 19.3–35.0 ms) longer than 21.1 ms (95% CI 18.7–24.4 ms) in patients with metachronous MBC p=.14. Which may be explained by those patients with synchronous MBC showed a significantly prolonged PFS after first-line treatment compared with those who had received adjuvant and/or neoadjuvant chemotherapy [16].

Dawood et al studied 3524 MBC patients and proclaimed that median OS among women with relapsed and de novo stage IV disease was recognized to be 27.2 and 39.2 ms, respectively, with this difference being statistically significant ($P < 0.0001$), that the administration of adjuvant therapy preceding recurrence might decrease survival after metastasis by selecting for resistant clones [17]

As regards HER2 expression, in multivariate analysis in our study HER2 negative expression has a good predictive value on OS than positive (HR =0.54;95% CI 0.29 – 0.98; P=0.045), which was not

matching with Lobbezoo et al study which reported that HER2 negativity was a bad prognostic factor on OS (HR= 1.44; 95%CI=1.13-1.83 P=0.003) (16). this may be explained by the utilization of anti-HER2 therapy which changed outcome of HER2-positive breast cancer to the extent that HER2-positive status is nowadays a prognostic factor associated with a favourable outcome in breast cancer [18].

Conclusion:

The increased use of anthracyclines and taxanes in the earlier stages of disease makes treatment selection in the second- and later-line settings more challenging and drug resistance often limits therapeutic options. the response rate and PFS of first-line therapy and adjuvant chemotherapy were important prognostic factors for survival. In addition, synchronous metastasis is associated with longer OS. Prospective cohort studies are needed to assess QoL and toxicity of different types of chemotherapy regimens.

Abbreviations:

ASCO	American Society of Clinical Oncology
CR	Complete Response
DM	Distant Metastasis
DFI	Disease Free Interval
ER	Estrogen Receptors
HER2	Human Epidermal Growth Factor Receptor
HR	Hormonal Receptor
PR	Progesterone Receptor
MBC	Metastatic Breast Cancer
Ms	Months
mPFS	median Progression Free Survival
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive disease
PFS	Progression Free Survival
QoL	Quality of Life
RD	Regressive Disease
RECIST	Response Evaluation Criteria in Solid Tum
SD	Stationary Disease
SECI	South Egypt Cancer Institute
TNBC	Triple Negative Breast Cancer

Conflicts of interest:

There are no conflicts of interest.

Authors' contributions:

This work was carried out in collaboration among all authors. Authors Adel Gabr and Hanan.A.Eltyb designed the study, performed the statistical analysis, and wrote the protocol. Author Nada.M.Hussien collected the patients data and wrote the final draft.

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