RESEARCH ARTICLE

Clinical Outcome of Turkish Metastatic Breast Cancer Patients with Currently Available Treatment Modalities - Single Center Experience

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Abstract

Background: Breast cancer is the most common malignancy and the second leading cause of cancer-related death among women in the developed countries. Despite advances in screening, improved local therapies and adjuvant systemic treatments, median survival of metastatic breast cancer patients (MBC) is in the range of 2-3 years at most. We aimed to investigate whether the prognostic factors and therapeutic responses of our Turkish patients are similar to those in the literature. Materials and Methods: We reviewed the medical records of MBC patients who had been treated in our institution between 1999-2009 and analyzed their clinicopathological features and survival outcomes retrospectively Results: A hundred and sixty patients were included. Median age was 47 (23-82), median follow up was 24 (2-186) months. At the time of diagnosis 59% of patients were under the age of 50 and 46% were postmenopausal. The majority (37%) had multiple sites of metastases. Forty percent received endocrine therapy and 40% chemotherapy as first line metastatic treatment. Thirty (20%) patients were treated with molecular targeting agents like trastuzumab, lapatinib and sunitinib, frequently combined with a chemotherapy agent. Five-year overall survival (OS) was 32% and median OS was 38 months for the whole group. Five year progression free survival (PFS) was 10% and median PFS was 10 months. Menopausal status, hormone receptor expression and disease free status had a significant impact on overall survival in the multivariate analysis (p 0.018, p 0.018 and p:0.003, respectively). Conclusions: All our patients were treated with the modern oncologic therapies recommended by the international guidelines. From our data, MBC patients live up to 3-4 years, indicating that further improvement beyond that requires development of new treatment modalities. The survival outcomes of our patients were consistent with the data reported in the literature.

Keywords: Metastatic breast cancer - chemotherapy - targeted therapy - survival outcomes - Turkey

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Introduction

Breast cancer is the most common malignancy and the second leading cause of cancer-related death among women in the developed countries (Smigal et al., 2006; Brewster et al., 2008). The increase in breast cancer incidence through the 1990's was seen mostly in early stage invasive and in situ cancers, and was attributed to increased detection of early stage disease with screening. After 2000's a decline in breast cancer incidence was reported probably due to the reduction in postmenopausal hormone therapy (Breen et al., 2007; Glass et al., 2007; Ravdin et al., 2007; Robbins and Clarke, 2007; Chlebowski et al., 2009).

The median survival for patients with metastatic breast cancer (MBC) appears to have improved over time, a trend which has been attributed to the availability of new, more effective agents, including taxanes, aromatase inhibitors, and trastuzumab (Gennari et al., 2005; Chia et al., 2007). However, despite improvements in systemic therapies MBC is still unlikely to be cured by any means. The primary goals of therapy are to prevent and palliate the symptoms of patients, to improve the quality of life and to delay the progression of the disease.

Although the overall survival (OS) of MBC patients ranges from a few months to many years, it has been reported to extend to 24 months with modern chemotherapies and to 40 months with targeted therapies (Aaltomaa et al., 1992). Only 5 to 10 percent of patients may survive more than 5 years. A number of clinical and biological prognostic factors are associated with long term clinical outcomes among women with MBC. Patients with good performance status, limited metastatic disease and who have longer disease free interval (DFI) tend to have better median OS (Stadtmauer et al, 2000).

Biologic markers, such as hormone receptors,

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human epidermal growth factor receptor 2 (Her-2) overexpression, and tumor burden have both prognostic and predictive value and are important factors in selecting appropriate treatment. The receptor status of metastatic sites differs from that of the primary in about 20 percent of cases (Kuukasjarvi et al., 1996; Macfarlane et al., 2012). In general, a biopsy is indicated at the time of first suspected recurrence in women with a prior history of breast cancer (Osoba, 1995).

Patients who have estrogen and/or progesterone receptor (ER/PR) positive tumors have a chance of 50 to 60 percent response rate to endocrine therapy in the first line setting. Although response rate declines by time it is approximately 20 to 30 percent in the second and third lines (Buzdar et al., 1996; Dombernowsky et al., 1998).

Breast cancer is one of the most chemotherapy-sensitive solid tumors. Active agents (anthracyclines, taxanes, vinorelbine, alkylating agents, antimetabolites) all target various cell cycle components, especially DNA and RNA synthesis. A different mechanism of action is exploited by biologic agents such as trastuzumab, lapatinib and bevasizumab.

There are several studies comparing the efficacy of these agents in monotherapy or combined therapies. First line multidrug chemotherapy in MBC is associated with higher response rates (RRs), longer PFS and a modest, if any, improvement in OS compared with sequential single-agent treatment (Carrick et al., 2009).

Approximately 20% of breast cancers overexpress Her-2. Overexpression of this receptor is associated with increased disease recurrence and worse prognosis. Discordant Her-2 expression in the primary and metastases has been reported in up to 20% of cases (Gancberg et al., 2002; Gong et al., 2005; Zidan et al., 2005). Because of this, it is advised to reanalyze Her-2 expression on biopsies obtained from newly recurrent metastases. High levels of Her-2 overexpression identify patients who might benefit from drugs that target Her-2, such as trastuzumab and lapatinib (Rusnak et al., 2001; Xia et al., 2002). First line treatment with the combination of trastuzumab and chemotherapy resulted in significantly higher overall RR and significantly longer PFS and OS (Slamon et al., 2001). Therefore, trastuzumab combination is the standart treatment of MBC in the first line setting. Lapatinib, an orally active dual erbB-1/2 thyrosine kinase inhibitor, has activity in trastuzumab-reftractory advanced disease. The combination of capecitabine and lapatinib was found to be active in the treatment of MBC patients who had received prior therapy with an anthracycline, a taxane and, trastuzumab (Cameron et al., 2008).

In Turkey, clinical and demographic characteristics of breast cancer patients, as described above, are not well known. We aimed to investigate whether the prognostic factors and therapeutic responses of our patients are similar to the literature.

Materials and Methods

We reviewed the medical records of MBC patients who had been treated in our institution between 1999-2009 and analyzed their clinicopathological features and survival outcomes retrospectively. Patients who had MBC at diagnosis and patients with early stage breast cancer who had relapsed during follow-up were included in this study. We recorded patient- (age, menopause), tumor- (size, grade, hormone receptors, Her-2 expression, and metastatic site) and treatment- (chemotherapy agents, targeted therapies) related characteristics and analyzed the clinical outcome.

Statistical analysis

Analysis was performed by using SPSS version 17.0 SPSS. PFS was defined as the time from the date of MBC diagnosis until disease progression or death from other causes. OS was measured from the date of MBC diagnosis to the date of death from MBC; surviving patients were censored at the date of last contact. The PFS and OS rates were calculated by Kaplan-Meier method. Cox regression analysis was used for multivariate analysis. A p value of 0.05 was considered statistically significant.

Results

A hundred and sixty patients were included in this study. Median age was 47 (23-82), median follow-up was 24 (2-186) months. The pathological and clinical characteristics of patients are shown in table 1. At the time of diagnosis 59% of the patients were under the age of 50 and 46% were postmenopausal. Thirty six percent of patients had MBC at diagnosis. The other patients had early stage disease at diagnosis and had relapsed during follow-up. The majority of tumors were invasive ductal

Table 1. Clinical and Pathological Characteristics

Clinical features		n	%
Age		23-82 (median 47)	
Age	≥50	66	41
	<50	94	59
Menopausal status	Premenopausal	87	54
	Postmenopausal	73	46
Stage at diagnosis	Early	90	56
	Locally advanced	12	8
	Metastatic	58	36
Pathological features			
Histology	IDC	125	82
	ILC	9	6
	Mixed (IDC+ILC)	12	8
	Others	7	4
Grade	1	0	0
	2	73	56
	3	57	44
Nodal metastasis	Positive	66	79
	Negative	18	21
Her-2 neu	0	60	37
	1	9	6
	2	9	6
	3	21	13
	Unknown	61	38
Hormone receptors	ER (+) /PR (+)	83	57
	ER (+) /PR (-)	18	13
	ER (-) /PR (+)	12	8
	ER (-) /PR (-)	32	22

IDC: invasive ductal cancer; ILC: invasive lobular cancer; ER: estrogen receptor; PR: progesterone receptor

cancer (82%) and high grade tumors. Estrogen and/or progesterone receptors were positive in 78% of tumors. Rebiopsies were performed from metastatic sites in 20 patients. There was 40% (8/20) discordans between primary tumor and metastatic site.

In early stage breast cancer patients, Her-2 expression was evaluated by immunhistochemistry (IHC) in 62% of tumors (n=99); among them 13% (n=21) had 3+, 6% (n=9) had 2+ score and 43% had a negative score (0 or 1+). Her-2 was unknown in 38% (n=61) of patients at diagnosis. Biopsies from metastatic site were performed in 25 patients for Her-2 expression. Totally 24% of tumors had Her-2 expression in primary or metastatic site by IHC and/or FISH.

A hundred patients who had early stage or locally advanced disease received adjuvant chemotherapy and/or endocrine therapy. Fifty four % of these patients received anthracycline based chemotherapy, 34% received anthracycline and taxane based chemotherapy. As adjuvant endocrine therapy, aromatase inhibitors, tamoxifen and tamoxifen plus luteinizing hormone-releasing hormone (LHRH) analogues were used in 24%, 76% and 11% of patients respectively.

Thirty one percent of patients with early stage BC had metastatic disease before 24 months of follow-up. Majority of the patients (37%) had multiple sites of metastases, 28% had only bone metastasis, 25% had visceral metastasis. Among those patients with only visceral metastasis, majority had lung (37.5%) and liver (37.5%) metastasis (Table 2). Two patients with lung metastasis had metastasectomy operation and no evidence of disease during follow-up, therefore these patients were not included in PFS and OS analysis.

Table 2. DFI and Sites of Metastases

		n	%
DFI	≤ 24 ay	31	31
	> 24 ay	69	69
Metastatic site*	Bone	45	28
	Soft tissue	15	9
	Visceral	40	25
	Unresectable local	2	1
Visceral metastases	Lung	15	37.5
	Liver	15	37.5
	Cranial	2	5
	Multipl visceral	4	10
	Pleura±pericard	4	10

*The other 37% of patients had multiple sites of metastases (bone±soft tissu±visceral)

Table 3. Treatment Characteristics and Response Rates to First Line Treatment

		n	%
First line therapy	Chemotherapy (CT)*	64	40
	Endocrine therapy (ET)	64	40
	CT+Trastuzumab	23	14
	ET+Trastuzumab	1	1
	CT+Sunitinib	4	3
	Lapatinib	1	1
	Sunitinib	1	1
Response to first line therapy**	Complete response	8	5
	Partial response	51	33
	Stable disease	49	31
	Progressive disease	48	31

* Sixty nine percent of patients (n: 44) received multiple agent CT, 31% (n:20) received one agent CT, **Two patients died due to the side effects of CT and were not included in response criteria

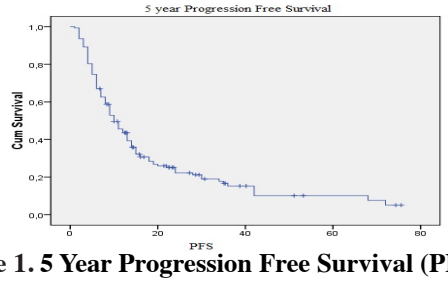

Figure 1. 5 Year Progression Free Survival (PFS)

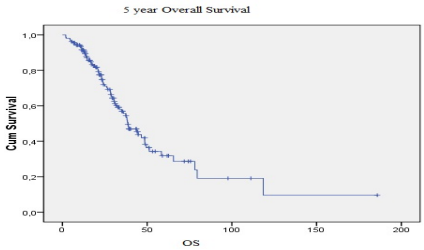

Figure 2. 5 Year Overall Survival (OS)

Treatment characteristics are shown in Table 3. Patients with bone metastasis, soft tissue metastasis and no life threatening visceral metastasis received endocrine therapy in the first line treatment (40% of patients). The majority of these patients were treated with an aromatase inhibitor. Forty percent of patients received chemotherapy in the first line treatment. The majority of these patients (69%) were treated with multiagent combined chemotherapy. The most commonly used chemotheray regimens were docetaxel, CEF, docetaxel plus epirubicin, weekly paclitaxel and capecitabine. Twenty percent of patients (n=30) received targeted therapies like trastuzumab, lapatinib and sunitinib, frequently combined with one of the chemotherapy agents. Twenty three of these patients were treated with trastuzumab and chemotherapy combination.

The response rates to first line treatment are shown in Table 3. There was progression in 31% of patients. Partial response and stable disease was observed in 33% and 31% of patients respectively. Complete remission was observed in eight (5%) patients.

Median PFS was 10 months. Five year PFS was 10%, 2 year PFS was 25% (Figure 1). Seventy two of 158 patients died during follow-up; 70 patients died because of disease progression, 2 patients died due to the side effects of chemotherapy. Five year OS was 32%, median OS was 38 months for the whole group (Figure 2).

Menopausal status, hormone receptors and DFI (≤24 months or >24 months) had significant impact on OS in multivariate analysis (p 0.018, p 0.018, and p 0.003 respectively). The number of agents used in the first line chemotherapy had impact on PFS (p 0.03), but no impact on OS (p 0.6).

Discussion

Although impressive improvements have been made in the adjuvant treatment of early stage breast cancer, approximately 20% of patients initially diagnosed with

regional stage disease will develop MBC (Chlebowski et al., 2009). In addition, metastatic disease is diagnosed at presentation in 1 to 5 percent of women. Despite advances in screening, improved local therapies and adjuvant systemic treatments, median survival of MBC patients is in the range of 2-3 years at most. In our study, 36 % of patients had MBC at diagnosis. In our country, despite screening programs the rate of early stage breast cancer is still low; the rate of MBC patients is higher than reported in the literature. Patients should be informed more in terms of screening and early diagnosis.

Metastatic breast cancer patients are treated according to the results of phase III clinical trials and international guidelines, in our clinic. In this study when we look at the entire group as a whole, median PFS was 10 months, OS was 38 months. Our results are consistent with the literature, even a little bit better than the international studies. We should keep in mind that this is a retrospective study and the included patients have different pathological, clinical and treatment characteristics.

In the first line setting, 69% of the patients received combined chemotherapy agents. The most commonly used single chemotherapy agents were docetaxel (75-100mg/m^2/q21d), paclitaxel (80mg/m^2/qw) and capecitabine (800-1250mg twice daily-14 days/q21d). The most commonly used combined regimens were CEF, Docetaxel+Epirubicin, and Docetaxel+Capecitabine. PFS of patients who received single agent chemotherapy was 6 months, median OS was 29 months. Patients who received combined agents had PFS of 13 months and OS of 45 months. In univariate analysis, number of chemotherapy agents (single vs combined) had statistically significant effect on PFS (p 0.03). Although there was 15 months of difference between OS of both groups it was not statistically significant. This may be due to the small number of patients who received chemotherapy. Clinical trials with newer agents have found a modest improvement of OS with combined agents but reported higher toxicity (Norris et al., 2000; O'Shaughnessy et al., 2002; Martin et al., 2007). Most trials compare single agent vs combination instead of comparing sequential use of these drugs. The modest OS benefits may not have been seen if crossover had been allowed (Sledge et al., 2003; Alba et al., 2004; Soto et al., 2006). In 2009 Cochrane metaanalyses, first line combination chemotherapy was associated with higher ORR and PFS. There was also 12% relative improvement in OS (Carrick et al., 2009). Despite these data, superiority of multi-agent chemotherapy over single agent is still controversial.

Forty percent of our patients who had hormone receptor positive tumors received first line endocrine therapy. Endocrine therapy was given to the patients with bone or soft tissue metastases and asymptomatic or minimally symptomatic visceral metastases. Majority of the patients (26%) were treated with aromatase inhibitors. In the first line endocrine therapy, the superiority of aromatase inhibitors over tamoxifen has been proved in both PFS and OS (Robertson et al., 1999; Nabholtz et al., 2000; Donneterre et al., 2000; Milla-Santos et al., 2003; Mouridsen et al., 2003; Paridaens et al., 2008). PFS has been reported 6-8 months with tamoxifen and 7-11 months with aromatase inhibitors. OS is about 40 months with both agents (Robertson et al., 1999; Nabholtz et al., 2000; Donneterre et al., 2000; Milla-Santos et al., 2003; Mouridsen et al., 2003; Paridaens et al., 2008) (32-37). In our study PFS was 12 months, OS was 47 months in patients who received first line endocrine therapy. Our results are a little better than the results reported in the literature. This can be explained by the higher ratio of ER and PR positive tumors (57%), low number of Her-2 positive patients and low number of patients with multiple visceral metastases (10%).

Combination of endocrine therapy with molecularly targeted agents also appears to be an effective treatment strategy, even in second line therapy. The benefit of everolimus plus exemestane in patients who had progressed with anastrozole was shown in the Bolero-2 trial (Baselga et al., 2012). Targeted agents combined with endocrine therapy will be used much more in the future.

Triple negative breast cancer, defined by the absence of ER, PR and Her-2, accounts for approximately 20% of breast cancers and is more commonly diagnosed in women less than 40 years. (Swain, 2008; Trivers et al., 2009). These tumors tend to behave more aggressively than other types of breast cancer. Unlike other breast cancer subtypes, there are no targeted therapies available, other than the administration of chemotherapy. In our study, due to the small number of patients with triple negative breast cancer, it has not been possible to analyze the outcomes of these patients.

In multivariate analysis, receptor status and DFI were significantly associated with PFS. They are both prognostic factors in MBC (Beslija et al., 2009). It has been shown that the clinical courses of receptor positive and negative tumors are different starting from early stage of disease (Saphner et al., 1996). In patients with hormone receptor positive tumors first line endocrine therapy is as effective as chemotherapy (Robertson et al., 1999; Nabholtz et al., 2000; Donneterre et al., 2000; Milla-Santos et al., 2003; Mouridsen et al., 2003; Paridaens et al., 2008). The median PFS was 11 months and 6 months for receptor positive and negative tumors, respectively (p 0.035). In our study, receptor status was one of the factors significantly associated with OS (p 0.018).

DFI is another prognostic factor effecting OS (Nicolini et al., 2006). In our study, PFS was 9 months and 6 months respectively for groups that has DFI ≥24 months and <24 months. DFI was also significantly associated with OS in both univariate and multivariate analysis. Median OS was 24 months and 45 months respectively for groups that has DFI <24 months and ≥ 24 months (p 0.014).

Approximately 20% of patients received first line targeted therapies. Patients who received trastuzumab in the first line setting had 9 months of PFS and 29 months of OS. In the trastuzumab studies, addition of single agent chemotherapy to trastuzumab provided 7-11 months of PFS and 25-36 months of OS (Slamon et al., 2001; Robert et al., 2006; Burstein et al., 2007; Valero et al., 2011). Our results are consistent with the literature. We know that Her-2 is associated with poor prognosis. Patients with Her-2 positive tumors have 4 months of PFS and 20 months of OS when they receive only chemotherapy, not treated

with trastuzumab (Slamon et al., 2001). In our group, all patients with Her-2 positive tumors received trastuzumab. PFS was 11 months, OS was 39 months in patients with Her-2 negative tumors. Although it was not statistically significant, poor prognostic effect of Her-2 was seen in both PFS and OS.

Five patients received sunitinib in the context of a clinical trial. Lapatinib was not approved for metastatic breast cancer before 2009 in our country. Therefore, small number of our patients received these agents and it has not been possible to compare our results.

In conclusion, the results of our study are compatible with survival data in the literature, even can be interpreted as a little better. Our study is a retrospective study and selected group of patients are included in the study; these are probably the main reasons for better results

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