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Treatment approaches for metastatic breast cancer in Turkey

BREAST CANCER PRACTICE PATTERN STUDY GROUP

ABSTRACT

Until today, a widely accepted treatment approach has not yet been defined for metastatic breast cancer. A non-comparative, non-interventional observational study was conducted to evaluate first-line systemic treatment approaches in metastatic breast cancer patients in Turkey. A total of 372 metastatic breast cancer patients from 34 institutes were taken into the study. Median age at diagnosis was 50 (21-84). Sixty-five percent of the patients were postmenopausal. Thirty percent were metastatic at first admission, the median time to metastasis for the rest was 28.5 months (3-205). Hormone receptor status was evaluated in 71% of patients and 57% were found receptor (+). Hormonal therapy was not considered in first-line for 32% of receptor (+) patients. For patients who were metastatic at first admission, anthracycline-based regimens were the most common choice of treatment as first-line. Overall in the first-line, taxanes were preferred for 13% and 8% of premenopausal and postmenopausal patients, respectively. Receptor status was found to significantly affect the choice of treatment for all subgroups, while age of onset and site of metastasis were significant for only postmenopausal patients.[Turk J Cancer 2005;35(2):61-69].

KEY WORDS:

Metastatic breast cancer, systemic treatment

INTRODUCTION

Breast cancer is the most prevalent cancer in women around the world (1). Its incidence increases by age. Although this increase continues in the postmenopausal period, its rate slows down. Approximately 183,000 women are diagnosed with breast cancer in the USA and 41,000 women die because of breast cancer annually (2). There is a great deal of evidence indicating hormonal impact on breast cancer etiology (3). About 5-10% of all breast cancer cases have a hereditary nature (4). Due to the increasing number of patients diagnosed at earlier stages, and higher cure rates in those patients treated with appropriate local therapies, mortality rates are consequently decreasing in recent years in developed countries such as the USA, the UK and Sweden (2). However, many patients in this group have micro-metastases, which cannot be clinically detected. Patients who do not receive systemic therapy are more likely to develop distant metastases (5).

The primary objective in metastatic breast cancer is palliation. The goals of therapy are to improve quality of life and to extend survival (6). Although median survival time is reported to be 2-3 years, longer survival can be observed in certain patients (7). Systemic therapy alternatives (hormonal therapy and/or chemotherapy) constitute the primary treatment of metastatic breast cancer. Radiotherapy and surgery can be utilized in localized symptomatic metastases with limited indications.

Currently, no chemotherapy regimen has been shown to be clearly superior to others in metastatic breast cancer, but anthracycline or taxane-based combinations have demonstrated some advantages in terms of objective response rates and time to progression, which may reflect on overall survival (8,9). Rate of disease progression, presence of co-morbid conditions, patient and physician preferences determine the choice of chemotherapy. Different regimens can be used consecutively in patients with relapse.

Although different consensus reports such as St. Gallen, NIH (National Institute of Health) or EUSOMA (European Society of Mastology) are guiding treatment approaches to early breast cancer, a widely accepted standard therapy selection criteria has not yet been defined for advanced breast cancer. There are some local guidelines prepared by large centers in Turkey to assist the treatment of metastatic breast cancer patients, however, treatment principles and administration can vary from one center to another. On the other hand, due to certain technical obstacles experienced in determination of hormone receptor status, there are discrepancies in assessment of tumor receptor positivity (estrogen and progesterone receptors) between different centers. Consequently, the data on receptor status in this patient population in Turkey is rather inadequate.

This observational study aimed at ascertaining the range of treatment approaches in metastatic breast cancer, as well as establishing the factors affecting treatment preferences. Furthermore, hormone receptor status in patients with metastatic breast cancer was investigated.

PATIENTS AND METHODS

As the purpose of the study was to determine nation-wide practice patterns in metastatic breast cancer treatment cross-sectionally and to investigate receptor status in the same group of patients, a non-comparative, non-interventional, observational study design was selected. Treatment selections were left completely up to the physicians' decisions, without any limitations or suggestions.

Stage IV metastatic breast cancer patients older than 18 years old, who were diagnosed with distant metastasis for the first time (either those who were metastatic at first admission or those who received therapy for early breast cancer and were newly diagnosed with metastasis) and had given written informed consents were included in the study. Patients were excluded only if they were enrolled in the study from another center or participated in another study on breast cancer.

Efficacy and safety parameters were not taken into consideration as the study aimed at establishing the existing tendencies. Time from first diagnosis, disease stage at first admission, time from diagnosis of first distant metastasis and other relevant parameters (family history, previous hormone replacement therapy, menopausal status, history of benign breast disorders, receptor status) were assessed. The variety of systemic treatment alternatives and the criteria for treatment selection were examined. A further analysis on hormone receptor determination rate in Turkey and the impact of receptor status on treatment preferences was made, based on the receptor status of this group of patients.

The statistical methods employed in this study are mostly of descriptive nature. Mean, minimum, maximum values, and when necessary simple ratio (%) were used in interpreting the data. The differences between the groups were analyzed by chi-square test for assessment of factors, which have an impact on treatment selection. P values of <0.05 were considered statistically significant.

RESULTS

A total of 372 patients referred to 34 institutions and clinics nationwide from October 2001 to June 2002 were enrolled in the study. Median age at diagnosis and median age for the onset of metastasis were 50 (21-84) and 52 (21-85), respectively. Excluding 113 patients (30.4%) who were metastatic at first presentation, median time to metastasis was 28.5 months (3-205) for the remaining 259 (69.6%) patients.

Patient and tumor characteristics are summarized in table 1. Of the patients, 9% had a familial history of breast cancer, 13% had received previous hormone replacement therapy (HRT), 4% had a benign breast disorder. It was established that two-thirds of the patients were postmenopausal.

Solitary metastases were detected in 90 (24%) patients, while the rest had multiple organ/tissue involvement. The most frequent sites of metastasis were bone (44%), lung (38%) and liver (32%) (Table 2).

When the receptor status of the patients was assessed, it was observed that receptor detection rates for estrogen and progesterone receptors (ER and PR) were 71% and 64%, respectively. Fifty percent of patients were found to have ER (+) tumors, while 46% of tumors were PR (+). The ratio of the patients who were positive for at least one of the hormone receptors (HR-positive) was 57% (Table 3).

When compared to premenopausal women, receptor positivity in postmenopausal women was significantly higher (63% vs. 47%; p=0.015).

Upon assessing the systemic therapy alternatives administered to the patients over the metastatic period, it was noted that 85% of the premenopausal patients received systemic chemotherapy, while 30% of the same group received hormonal therapy. Combined chemo-hormonal therapy was given to 15% of the patients (Table 4). When chemotherapy regimens administered to the premenopausal patients were examined, it was established that 63% of the patients received non-taxane containing anthracycline regimens, regardless of clinical stage at presentation. Taxane containing regimens were used in 33% of the patients. Only 2% received CMF (cyclophosphamide, methotrexate, fluorouracil), while another 2% of the patients were administered cisplatinum-based regimens.

Hormonal therapy methods significantly varied for premenopausal patients. Of the 36 patients who received hormonal therapy, 20 (56%) underwent surgical or medical castration. Tamoxifen and aromatase inhibitors (AI) were used in 19 (53%) and 10 (28%) patients, respectively. AI's were used following castration in only 6 patients, following chemotherapy in 2 patients and as single-agent therapy in 2 patients.

When compared to premenopausal patients, the postmenopausal patients had lower rates of use of chemotherapy alone (51%) and overall use of chemotherapy (74%) (Table 4). Non-taxane containing anthracycline combinations were preferred for 50% of the patients, while 35% received taxane-containing regimens. Various combinations of vinorelbine were used for 7%, whereas CMF and cisplatinum-based regimens were preferred for 4% and 3% of the patients, respectively. The use of AI's was about twice as much as the use of tamoxifen in the postmenopausal group, including the patients who received combined chemo-hormonal therapy (76 vs. 37 patients).

The analysis was repeated with the subgroup of patients who were metastatic at first admission (n=113) in order to obtain a more objective assessment of taxane use, since its use was found to be higher than predicted in the whole group. Anthracycline-based regimens were observed to be the treatment of choice in 85% of the premenopausal and 75% of the postmenopausal subjects as first-line therapy. Taxanes were used for 13% and 8% of the premenopausal

Table 1
Patient and tumor characteristics (n=372)

	Number	Percentage
Stage at Diagnosis		
I	18	4.8
II	127	34.1
III	94	25.3
IV	113	30.4
Not known	20	5.4
Family history of breast cancer		
Yes	33	8.9
No	338	90.9
Not known	1	0.2
HRT use		
Yes	48	12.9
No	318	85.5
Not known	6	1.6
Benign breast disorder		
Yes	16	4.3
No	346	93.0
Not known	10	2.7
Menopausal Status		
Premenopausal	130	34.9
Postmenopausal	242	65.1

and postmenopausal patients, respectively, as first-line therapy.

A similar sub-group analysis was conducted to assess the first-line hormonal therapy preferences in postmenopausal patients. Hormonal therapy was administered to 28 of 65 postmenopausal patients who were metastatic at the time of diagnosis. AI's and tamoxifen were used for 17 (60%) and 11 (40%) of those patients, respectively.

Receptor status had a significant impact on treatment choice for both premenopausal and postmenopausal patients ($p<0.0001$ and $p<0.0001$, respectively) (Table-5). It was observed that 86% of the premenopausal patients, whose receptor status were not identified, received chemotherapy alone. Hormonal therapy was administered to 57% of HR (+) patients, while 43% of the same group received chemotherapy alone. In the group of HR (-) patients, 9% received hormonal therapy following chemotherapy and 2% received hormonal therapy alone.

Unlike premenopausal patients, 55% of postmenopausal group, whose receptor status were not known, received hormonal therapy and use of chemotherapy alone for this group was 45%. Hormonal therapy was administered in 72% of HR (+) patients, and the use of chemotherapy alone for this group of patients was 28%. Only 8% of the HR (-) postmenopausal patients received hormonal therapy.

The physicians participating in the study demonstrated a higher preference for chemotherapy in patients with abdominal visceral or soft tissue metastases when compared to isolated bone or brain metastases. This difference was significant in the postmenopausal group (65% vs. 46%; $p=0.001$), whereas it was merely a tendency for the premenopausal patients (78% vs. 64%; $p=0.114$).

For the patients at 65 years of age or older, chemotherapy

Table 2
Patients enrolled with respect to site of metastasis
(n=368; site of metastasis is not determined in 4 patients)

Site of Metastasis	Number	Percentage
Bone	161	44
Soft tissue	84	23
Lung	141	38
Liver	118	32
Brain	10	3
Other	48	13

Table 3
Hormone receptor status of the patients whose receptor status were determined (n=247)

	ER*		PR**		HR	
	n	%	n	%	n	%
Positive	122	50	99	46	141	57
Negative	124	50	115	54	106	43

**ER determination rate is 71%*

***PR determination rate is 64%*

use was significantly lower than hormonal therapy (chemotherapy: 48% vs. 66%; p=0.003). Being under or above age of 40 has no impact on treatment choice for premenopausal patients (chemotherapy: 72% vs. 79%; p=0.15).

DISCUSSION

This study established therapeutic approaches in metastatic breast cancer management through the participation of 34 healthcare facilities nationwide.

The median age of the patients enrolled in the study was 50. It is a well-known fact that breast cancer incidence reaches a peak after the age of 50 (10). Therefore, median age of the participants can be expected to be higher than what was established. However, considering the fact that the course of the disease is more aggressive in patients diagnosed at younger ages and that all patients were metastatic, a lower median age than that of a general breast cancer population can also be reasonable. When the patients who were metastatic at time of diagnosis were excluded, the median time to metastasis was calculated to be 2.5 years, which is consistent with the fact that about 40% of the patients were at stage III at presentation. This time period is also consistent with EBCTCG meta-analysis, which underlines that majority of relapses occur within the first 5 years (11). The patients who were at stage I at presentation constituted about 5% of the cohort, which could be explained by the fact that the risk for metastasis is very low in this group when appropriate therapy is administered. Of all the patients, 30% were metastatic at presentation. This is merely the percentage of the patients who were metastatic at diagnosis in our study population and it cannot be generalized as a representation of all breast cancer cases in Turkey.

About 5-10% of all breast cancer cases are hereditary (4,10). Of all the patients, 9% had a family history of breast cancer in the study. This could be justified by lack of

Table 4
Systemic treatment preferences for premenopausal and postmenopausal patients

	Premenopausal		Postmenopausal	
	n	(%)	n	(%)
Chemotherapy	85	70	118	51
Chemotherapy + Hormonal Therapy	18	15	53	23
Hormonal Therapy				
Tamoxifen	4	3	14	6
Aromatase Inhibitor	2	2	46	20
Castration	2	2	-	-
Castration + Tamoxifen	4	3	-	-
Castration + Aromatase Inhibitor	6	5	-	-
TOTAL	121	100	231	100
Total Chemotherapy	103	85	171	74
Total Hormonal Therapy	36	30	113	49
Not reported	12		8	

documentation, high percentage of cases without diagnosis or diagnoses concealed by patients due to social concerns. Benign breast disorder history was established to be lower than predicted, possibly owing to similar reasons (10).

Consistent with the literature, the most frequent sites of metastasis were determined to be bone, lung and liver (10). Solitary isolated metastases were observed mostly in those three organs, in support of that result.

ER and PR statuses were not identified in 29% and 36% of the patients enrolled, respectively (Table 3). Technical means and differences in the institutions taking part in the study could be the leading reason for a substantial quantity of the patients' receptor statuses not being identified. In patients whose receptor status was examined, ER and/or PR (+) tumors was found to be 57%. Furthermore, HR (+) tumors were significantly prevalent in postmenopausal patients.

Receptor status is regarded to be an important prognostic factor. It can be considered normal to observe lower than expected receptor positivity rates in this study population as more aggressive course and increased relapse risk can be predicted with receptor negativity.

Systemic treatment approaches were assessed with respect to menopausal and receptor statuses. Of all the patients in the premenopausal group, 85% received systemic chemotherapy and 30% received hormonal therapy (combined chemo-hormonal therapy was 15%). The patients who were administered with chemotherapy and hormonal therapy constituted 74% and 49% of the postmenopausal group, respectively (combined chemo-hormonal therapy was 23%) (Table 4). These results confirm that hormonal therapy was utilized more frequently in the postmenopausal group when compared to the premenopausal patients.

When systemic therapy approaches were assessed with respect to receptor status, it was observed that receptor status had a significant impact on treatment choice for both premenopausal and postmenopausal patients. It was also noted that the physicians participating in the study had a tendency to consider premenopausal patients of unknown receptor status as HR (-), and treated 86% of these patients with chemotherapy alone. On the other hand, 43% of HR (+) patients were not considered for hormonal therapy. Unlike premenopausal patients, in the postmenopausal group, use of hormonal therapy for the patients of unknown receptor status was as high as 55%. Hormonal therapy was given to 72% of HR (+) postmenopausal patients (Table 5).

Table 5
Systemic treatment preferences for premenopausal and postmenopausal patients with respect to receptor status

	Premenopausal* (eligible 115 pts)			**Postmenopausal** (eligible 222 pts)**		
	Receptor Unknown N (%)	Receptor (+) N (%)	Receptor (-) N (%)	Receptor Unknown N (%)	Receptor (+) N (%)	Receptor (-) N (%)
CT	24 (86)	18 (43)	40 (89)	32 (45)	27 (28)	50 (92)
CT+ HT	2 (7)	10 (24)	4 (9)	24 (34)	27 (28)	2 (4)
HT	2 (7)	14 (33)	1 (2)	15 (21)	43 (44)	2 (4)
Total	28 (100)	42 (100)	45 (100)	71 (100)	97 (100)	54 (100)

HT: Hormonal therapy
CT: Chemotherapy
* *p<0.0001*
** *p<0.0001*

Hormonal therapy is known to be an important systemic therapy alternative both for early stage and metastatic breast cancer patients. Hormonal therapy, which has similar efficacy but fewer side effects when compared to chemotherapy, should be the treatment of choice except for the cases of life-threatening visceral metastatic disease, a symptom requiring rapid palliation or a condition which would not respond to hormonal treatment (5). Although receptor status is shown to be a significant factor to affect treatment preferences, 43% of premenopausal and 28% of postmenopausal HR (+) patients were not administered hormonal therapy. This fact indicates that this treatment alternative is not being employed, as it should be for patients who are candidates for hormonal treatment.

Chemotherapeutic agents demonstrated to be active in metastatic breast cancer can be listed as anthracyclines, taxanes, alkylating agents, fluoropyrimidines, antimetabolites, vinka alkaloids, platinum-based agents and mitomycin C. Combination regimens often administered are CAF (cyclophosphamide, doxorubicin, 5-FU), CMF (cyclophosphamide, methotrexate, 5-FU), AC (doxorubicin and cyclophosphamide) and docetaxel-doxorubicine (12-15).

It was observed that the participating physicians preferred chemotherapy regimens, which conformed to the literature. However, the use of taxane-containing regimens was more frequent than predicted, regarding first-line use (33% in premenopausal, 35% in postmenopausal patients). When the same analysis was carried out on the patients who were metastatic at presentation, the use of taxanes in premenopausal and postmenopausal patients was found to be 13% and 8%, respectively. This high percentage of taxane use in the overall population could be due to the fact that anthracycline-based regimens had been used previously in the adjuvant setting. In other words, taxanes are preferred more frequently in the first-line for patients who had undergone chemotherapy previously for early stage breast cancer and developed distant metastasis thereafter.

Oophorectomy, medical castration with LHRH agonists (goserelin) (in premenopausal patients), nonsteroid antiestrogens (such as tamoxifen, toremifen), AI's (anastrozole, letrozole etc.) (in postmenopausal patients) represent major hormonal therapy options (16-20). Recent studies have recommended the use of selective AI's as first-line hormonal therapy, regarding to their superiority against tamoxifen in terms of greater efficacy and fewer side effects in postmenopausal women (20,21). Patients who are eligible for first-line hormonal therapy and respond well can be given second or further lines of hormonal therapy if progression is detected. It has been demonstrated that tamoxifen is an effective alternative in the second-line hormonal therapy following first-line anastrozole treatment, confirming the recent change of hormonal therapy sequence in the advanced disease setting (22).

It is recommended that surgical or medical castration can be used as second-line therapy when tamoxifen is used in first-line for premenopausal women. On the other hand, when castration is used as first-line, tamoxifen should be given as second-line therapy and other hormonal therapies should be used as in postmenopausal women for the further treatment lines (23). However, recent randomized studies and their meta-analyses have demonstrated that combined hormonal therapies (LHRH agonist + tamoxifen) are more effective than use of either treatment alone (24). The concept of combined estrogen blockade is becoming increasingly common in breast cancer literature (25).

Aromatase inhibitors have been developed primarily for use in women whose ovarian function has ceased; in either natural or surgical postmenopausal patients (26,27). In premenopausal women, the ovary can overcome the estrogen blockade by reflex increments of luteinizing hormone (LH) and follicle stimulating hormone (FSH), so aromatase inhibitors become inactive when used alone in premenopausal women (28). Because of insufficient ovarian blockade in premenopausal women with breast cancer, the aromatase inhibitors must be combined with a gonadotropin releasing hormone (GnRH) agonist to prevent the reflex LH and FSH increments (29).

It was observed in the current study that hormonal therapy methods for premenopausal patients varied significantly, which could be a reflection on the fact that a consensus on standard treatment selection criteria for metastatic breast cancer has not been yet clearly defined. It can be presumed that these variations will diminish as the advantages of combined hormonal therapy become clearer in routine practice.

It was observed that AI's were utilized twice as frequent as tamoxifen in the postmenopausal patient cohort. As this could be due to the fact that tamoxifen had been used as adjuvant therapy in HR (+) patients previously who were not metastatic at presentation, the analysis was repeated on patients who were metastatic at first admission to establish whether there was a tendency for AI's. AI's were found to be preferred in 60% of eligible patients of this group, which demonstrated that the use of AI's was more prevalent than that of tamoxifen for advanced disease setting.

It was observed that site of metastasis was another factor to affect treatment selection by the participating physicians, in addition to menopausal and receptor statuses. Chemotherapy use is significantly higher in patients with visceral or soft tissue metastasis when compared to isolated bone or brain metastases in the postmenopausal group. There is no data showing that hormonal therapy is not efficient in treating visceral or soft tissue metastases. Chemotherapy seems to be selected primarily for the majority of metastatic breast cancer patients, although hormonal treatments have similar efficacy with fewer side effects, are recommended as treatment of choice unless there is an immediately life threatening visceral metastatic condition, and they are known to significantly improve quality of life (5,30). It is emphasized that giving precedence to hormonal therapy and delaying chemotherapy in metastatic patients has no negative effect on survival, on the contrary, survival can be potentially improved by prior hormonal therapy since it delays disease progression and the need for chemotherapy (30). Furthermore, it is recommended in Cochrane Review-2003 update that hormonal therapy should be preferred to chemotherapy for metastatic breast cancer patients with positive hormone receptors, with the exception of rapidly progressing diseases (31). Despite these suggestions, common prior use of chemotherapy in this patient group could be the result of giving a too broad interpretation to "life-threatening visceral metastasis".

Age was another factor bearing importance in the treatment choice for postmenopausal patients. Chemotherapy use was significantly lower than hormonal therapy for the patients at 65 years of age or older. This could be a consequence of lower chemotherapy tolerance in older patients. Being under or above age of 40 did not have a significant impact on treatment preference in premenopausal patients.

In summary, the results obtained in this study demonstrated that there was a wide range of therapy approaches employed by physicians in metastatic breast cancer therapy. The determinant factors were noted to be menopausal status, site of metastasis, patient's age and, although determination rates are lower than expected, receptor status. The majority of the chemotherapy regimens utilized were consistent with the literature. It was also observed that hormonal therapy was not considered to be the treatment of choice for a substantial part of the patients who had been known to be receptor positive. Although hormonal therapy has been demonstrated to be of comparable efficacy to chemotherapy and chemotherapy is associated with higher toxicity and lower quality of life, chemotherapy seems to be preferred more frequently than hormonal therapy for receptor positive metastatic breast cancer. This can be a result of interpreting the concept of "life-threatening visceral metastasis" more broader than it is actually meant.

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