

SHORT COMMUNICATION

Randomized Trial Comparing Locoregional Resection of Primary Tumor with No Surgery in Stage IV Breast Cancer at the Presentation (Protocol MF07-01): A Study of Turkish Federation of the National Societies for Breast Diseases

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■ **Abstract:** The MF07-01 trial is a phase III randomized controlled trial which compares breast cancer patients with distant metastases at presentation who receive locoregional treatment for intact primary tumor with those who do not receive such treatment. The primary objective of the study is to assess whether locoregional treatment of the primary tumor provides a better overall survival. Secondary objectives include progression-free survival, quality-of-life, and morbidity related to locoregional treatment. Locoregional treatments consist of either mastectomy or breast conserving surgery with level I-II axillary clearance in clinically or sentinel lymph node positive patients. Radiation therapy to the whole breast follows breast conserving surgery. Standard systemic therapy is given to all patients either immediately after randomization in no-locoregional treatment arm or after surgical resection of the intact primary tumor in locoregional treatment arm. The study is conducted in Turkey as a multicenter trial with central randomization. Total accrual target is 271. The trial was activated in October 2007 and authorized centers started to recruit patients since then. ClinicalTrials.gov identifier number is NCT00557986. ■

Key Words: breast cancer, metastasis, randomized trial, surgery, survival

The incidence of synchronized distant metastatic disease in newly diagnosed breast cancer (BC) patients is between 3.5% and 10% (1–3). BC with distant metastases is considered to be a disease with no cure. Therefore, surgical treatment of the intact primary is indicated only if it is symptomatic. Local complications such as bleeding, ulceration, pain, and hygienic disturbances are among the palliative indications for locoregional surgery. Systemic therapy is the choice of treatment in stage IV BC (4). However, recent encouraging reports challenged this classical

approach of “no-touch at uncomplicated primary.” So far, seven retrospective studies were published (one in an abstract form). All studies provided results of retrospective cohorts which are evaluated with or without controls (level 3 and level 4 study designs). All studies concluded that resection of the primary tumor in stage IV BC patients translates into a considerable survival advantage (1–3,5–8). Given insufficient evidence to reach a clear conclusion in the current debate, all studies conclude that a well-designed, randomized controlled trial should be conducted to determine the impact of locoregional treatment in these patients.

The MF07-01 trial is designed following emergence of retrospective reports assessing complete removal of primary tumor in stage IV BC patients. This article describes of this prospective trial is given in detail.

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MATERIALS AND METHOD

Description

The MF07-01 trial is a phase III, multicentric, randomized controlled clinical trial comparing locoregional treatment (complete resection of the primary tumor and when necessary, axillary clearance and radiotherapy to whole breast, thoracic wall and/or regional lymph basins) with no locoregional treatment in stage IV BC patients. All patients receive systemic treatment regardless of their study assignment. In locoregional treatment arm, systemic therapy is given after surgical extirpation of the intact primary tumor whereas in no locoregional treatment arm, systemic therapy is given immediately after randomization. The hypothesis of the present trial is that adequate locoregional treatment of the primary tumor as described above prolongs overall survival when compared with no locoregional treatment in stage IV BC patients.

Outcome

The primary aim of the study is to determine if locoregional treatment of the primary tumor provides a survival advantage in stage IV BC patients. Therefore, the primary endpoint of the study is overall survival. Secondary endpoints are progression-free survival, quality-of-life measures, and morbidity related to locoregional treatment.

Eligibility

All women with histologically proven BC and whose distant metastases are discovered at their first admittance are eligible for this study. All participating centers are required to obtain local ethics committee approval. Inclusion criteria include: primary breast tumor amenable for complete surgical resection, patients in good physical condition for receiving protocol driven locoregional and systemic treatments as well as patients eligible for sentinel lymph node (SLN) biopsy and receiving radiotherapy. Exclusion criteria include; primary tumor not amenable for complete resection (such as tumor extending to neighboring tissues; T4a,c or inflammatory breast cancer; T4d); primary tumor with extended infection, bleeding, or necrosis; patients with poor physical condition which prevents the patient from receiving protocol driven locoregional and systemic treatment; synchronous primary cancer at the contralateral breast; previous diagnosis of other cancers (excluding basal cell skin cancer, squamous cell skin cancer, and cervical intra-

epithelial neoplasia); clinically involved contralateral axillary nodes; patients not suitable for adequate follow-up; and failure to give informed consent.

Preliminary sample size calculation is based on survival figures from the largest retrospective study comparing stage IV BC patients who underwent surgical resection of primary tumor with those who did not. Kahn et al. (5) reported that absolute overall survival difference between two study groups was approximately 20% favoring surgical resection of the primary tumor. For a randomized clinical trial to compare survival between surgery and no surgery for BC, sample size was calculated under several different assumptions of event rates. After consideration of previous retrospective studies, the assumptive overall survival difference between two study groups is determined to be 18% (35% in locoregional treatment group versus 17% in no-locoregional treatment group). A 10% drop out rate including lost to follow up is assumed. By using a one sided log-rank test with a 95% confidence ($\alpha = 0.05$) and a 90% power ($\beta = 0.9$), sample size calculation revealed that 271 patients are needed to be randomized. Therefore 123 patients will be assigned to each study arm. The primary end point in this study is overall survival (OS) and analyses of OS included all deaths whether they are BC-related or not. First, baseline characteristics will be compared by group. Kaplan-Meier curves will be used to compare the survival of the two groups. Model assumptions will be tested. Cox regression analyses will be carried out secondarily to made adjustments for baseline characteristics that are unbalanced or are prognostic factors.

Randomization Procedure and Treatment Allocation

Randomization of subjects is done centrally by data center computer through internet. Patient randomization is only accepted from authorized investigators. No stratification is applied during randomization. Eligible patients are randomly assigned to two study arms; (a) locoregional treatment and (b) no-locoregional treatment. In no-locoregional treatment group, patients receive systemic therapy as indicated, whereas in locoregional treatment group, patients receive systemic treatment after they undergo surgical resection of the primary tumor. Locoregional treatment consists of complete resection of the primary tumor (either as mastectomy or breast conserving surgery; BCS),—if axillary nodes are involved—level I-II axillary clearance and radiotherapy to whole breast after BCS. All patients who are clinically node positive undergo

standard level I-II axillary clearance. Whereas in clinically node negative patients, SLN biopsy is allowed to assess axillary involvement. Axillary clearance is not required in patients with negative SLN. These patients remain as N0. In SLN positive patients, level I-II axillary clearance is required. All patients who undergo BCS receive radiotherapy to the whole breast for 30 days (including 5 days of boost delivery) as indicated in early stage BC. In the no-locoregional treatment group, primary tumor resection is only allowed whenever the tumor requires palliation (in conditions such as bleeding, ulceration, pain, etc.). All patients in both arms receive protocol driven standard systemic therapy. Patients who are assigned to no-locoregional treatment arm receive systemic treatment immediately after randomization, whereas patients who are randomized to locoregional treatment arm receive systemic therapy after their primary tumor is resected. In c-erb B2 negative patients, either doxorubicine (75 mg/m²) and docetaxel (100 mg/m²) are given sequentially (each agent is given consecutively for three cycles for every 3 weeks) or doxorubicine (75 mg/m²) and docetaxel (50 mg/m²) are given in combination for six cycles for every 3 weeks. The choice between sequential and combined treatment is decided individually by each institution. In patients whose disease shows progress under first-line chemotherapy, cisplatin plus gemcitabine or capecitabine will be given as the second-line systemic therapy. In c-erb B2 positive (IHC +++ positive or FISH positive) patients, the same chemotherapy regimen as it is given in c-erb B2 negative patients is administered along with trastuzumab. Trastuzumab is given to the patients for every 3 weeks until any disease progression is detected. Hormone therapy is given only to patients whose tumor expresses estrogen (ER) and/or progesteron receptor (PR). As hormone therapy, an LHRH analog and tamoxifen are given to premenopausal ER and/or PR positive patients whereas, aromatase inhibitors are given to postmenopausal ER and/or PR positive patients. Patients receive hormone therapy continuously until any disease progression is detected. In patients with bone metastasis, biphosphonate plus zelondronic acid or only ibandronate are given for every 3–4 weeks until any drug toxicity or patient deterioration is observed. Decisions to administer radiation therapy to the regional lymph basins, thoracic wall and metastatic bone regions are given by the each institution according to their individual treatment protocols. All radiation treatments are given fol-

lowing chemotherapy regardless of the randomization arm. All site specific treatment decisions regarding distant metastases are allowed to be made individually by each center. Patients may receive radiation therapy and/or gamma knife treatment for bone and cranial metastases. Centers may choose to resect intra-abdominal and intrathoracic metastases, if they regard the procedure is suitable.

Follow-Up

Women are followed for every 6 months until any disease progression or death is observed. Where appropriate, tumor markers (CA 15-3 and CEA), whole body bone scintigraphy, thoracoabdominal computerized tomography (CT) and/or magnetic rezonanse imaging (MRI), whole body positron emission tomography (PET)-CT are requested during each follow-up visit. Metastatic burden of distant sites, whether at diagnosis or during follow-up, is scored by CT. Turkish version of SF36-questionnaire is used to assess the patients' quality of life measures. This questionnaire is completed by the patient at randomization and every 6 months thereafter until endpoint is reached.

RESULTS

The MF07-01 trial was activated and patient recruitment was commenced in October 2007. Currently, seven oncology centers at the university or state hospitals in Turkey are enrolling patients for the MF07-01 study, and additional sites are waiting their ethic committee approval to start patient enrollment. First interim analysis of the study is planned to be done at the end of third year.

DISCUSSION

Retrospective analysis of the American National Cancer Data Base (NCDB) data indicated that resection of the primary breast tumor in patients with stage IV BC was associated with a significant survival advantage (5). They found that women who underwent removal of their primary breast tumor with tumor-free margins were found to have a superior overall prognosis with a hazard ratio of 0.61 when compared with women who did not undergo surgery. In a small retrospective study, Carmichael et al. (1) reported their single institution case series ($n = 20$) who underwent primary tumor resection for stage IV

BC at the presentation or were diagnosed with metastases within one month of surgery. They found that median survival after surgery was 23 months and half of the patients were alive with no local disease at 20 months. Because there was no control group to compare these results, no evident conclusion could be drawn for superiority of local control in this study. Gnerlich et al. (2) reviewed BC patients who are found to be stage IV at the time of their first admittance in SEER data between 1988 and 2003. They found that patients who underwent surgical removal of their primary tumor had a better survival compared with women who did not have surgery. Their results revealed that patients who had surgery were 37% less likely to die than the ones who did not undergo surgery. In 2006, Barbiera et al. (6) reported their institutional findings in a retrospective cohort of 224 patients who were diagnosed as stage IV BC with intact primary tumor. They found that removal of the primary tumor significantly improved progression-free survival in BC patients with distant organ metastases. However, in their analysis, the overall survival was not different between groups. Rapiti et al. (7) reported another retrospective study of 300 stage IV BC patients who were retrieved from Geneva Cancer Registry. They reported that women who had complete excision of the primary breast tumor with negative surgical margins had a 40% reduced risk of death compared with women who did not have surgery. In another similar study, Blanchard et al. reported a retrospective series of 427 patients with stage IV BC from their institutional registry (3). Their results revealed that the interval from diagnosis to death was 27 months for the surgery group in which patients underwent surgical resection of the primary tumor whereas it was 17 months for the no-surgery group. The difference between groups was found to be significant. More recently, Fields RC et al. reported their retrospective analysis of their institutional cohort of 409 patients with stage IV BC (8). This study provided further evidence that BC patients with distant metastases at diagnosis benefit from surgical excision of their primary lesion in terms of improved survival. After controlling for age, comorbidity, tumor grade, histology, and sites of metastasis, patients who underwent surgical resection were 47% less likely to die when compared with patients who did not undergo surgery for the primary tumor. The median overall survival was significantly longer in patients who had resection (26.8 months versus 12.6 months).

However, timing of the locoregional tumor resection varies in all studies. Reports which reviewed SEER or Geneva Cancer registry data provide us with limited information about the timing of surgery because patients underwent locoregional surgery of the primary tumor at any point in their course following their diagnosis. However, four different institutional studies stated that local surgery prior adjuvant therapy does have a role in controlling the primary cancer and controlling local symptoms with better survival rates than these who did not have surgical treatment in stage IV BC (1,3,9–11).

Nevertheless, all studies were subject to selection biases with regard to their retrospective nature. It was evident that surgeons were inclined to use surgery in patients who have more favorable features (i.e., younger age, smaller tumor size, less evident axillary involvement, fewer sites of metastasis) (6,7). Therefore, interpretation of these studies' results should be done with caution. Further limitations of these trials such as lack of information regarding radiation/systemic treatment, histopathologic feature, and timing of surgery of the intact primary were obvious.

It is suggested that a proper prospective study needs to include a design which assesses all aspects of the locoregional treatment for the primary tumor: surgical resection with tumor-free margins, axillary clearance, and radiotherapy (12). In our current prospective trial, we designed the experimental arm as they receive locoregional treatment which includes complete excision of the primary tumor (either with mastectomy or BCS with tumor-free margins), axillary clearance when lymph node involvement was evident and radiotherapy to whole breast after BCS. Rapiti et al. (7) found that the survival of patients who had surgery with involved surgical margins was not different from those of women who did not have surgery. In their study, they also reported that the surgical excision with clear margins led to a significantly better 5-year disease-free survival when compared with excision with involved margins (7). We believe this data justifies our current protocol which necessitates obtaining tumor-free margin during BCS. Regarding axillary disease control in stage IV BC patients, in the NCCDB study, although the extent of nodal disease was not significantly related to survival, women undergoing total mastectomy were expected to have nodal dissection to some extent. It is pronounced that this may have contributed to the survival advantage observed in the total mastectomy group (5). In the Geneva study, authors

found a trend toward improvement in survival for women who had both tumor-free surgical margin and axillary clearance (7). Similarly, regional radiotherapy data is lacking in previous series. In the Geneva registry study, whole breast radiotherapy was administered to patients who underwent BCS and they found that lack of radiotherapy increased the hazard of death independently (7).

To our knowledge, the MF07-01 trial is the first on-going randomized controlled trial aiming to assess the survival impact of resecting the primary tumor at diagnosis in stage IV BC patients. We believe that this trial will enable us to understand the role of locoregional treatment in these patients with more solid evidence. Moreover, its results will expand our knowledge about BC biology and mechanisms of metastasis. Since there are contradictory theories about the issue (13,14), our current study is expected to provide data which may explain how removal of the primary tumor would effect the tumor progression on clinical grounds.

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