Combined Modality Treatment of Locally Advanced Breast Carcinoma in Elderly Patients or Patients with Severe Comorbid Conditions Using Tamoxifen as the Primary Therapy

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BACKGROUND. The purpose of the current study was to evaluate the objective response rate and possibility of breast-conserving surgery using neoadjuvant tamoxifen in the multimodality treatment, including surgery and radiotherapy, of elderly or frail patients with locally advanced breast carcinoma.

METHODS. Forty-seven patients age $>$ 75 years or age $<$ 75 years with comorbid conditions and locally advanced breast carcinoma were treated with neoadjuvant tamoxifen (20 mg/day) for 3–6 months. This was followed by surgery and radiotherapy when feasible and adjuvant tamoxifen for 5 years or until disease recurrence.

RESULTS. The median age of the patients was 72 years (range, 48–86 years). Approximately 22% had T3 lesions, 57% had T4 lesions, 22% were Stage II (AJCC Manual for Staging Cancer, 3rd edition), and 78% were Stage III. Eighty percent were estrogen receptor positive. After 6 months of treatment with neoadjuvant tamoxifen, a response rate of 47% was observed, including a complete response rate of 6%. Twenty-nine patients (62%) were rendered free of disease by surgery, including 5 with breast-conserving procedures. After a median follow-up of 40 months, 23 patients (49%) remained disease free. The median survival time had not been reached at the time of last follow-up. No major toxicity was observed, with the exception of one patient who developed a possible tamoxifen-related Stage I endometrial carcinoma. The estimated 2-year and 5-year progression free and overall survival rates were 50% and 41%, and 83% and 59%, respectively.

CONCLUSIONS. The results of the current study show that neoadjuvant tamoxifen was effective in the treatment of elderly or frail patients with locally advanced breast carcinoma with estrogen receptor positive tumors, and resulted in a reasonable response rate, including complete responses and good overall survival. ***Cancer* 2000;88:2054–60.** © *2000 American Cancer Society.*

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Locally advanced breast carcinoma (LABC) remains a serious health problem in the world.[1] For decades local therapies (such as surgery and/or radiotherapy) were the treatment of choice, but results were poor due to the high frequency of distant recurrence,[2] which is why combined modality treatments (including systemic chemotherapy and hormonal therapy) became the standard of care for these patients.[3–5] Recently, more emphasis also has been placed on breast conservation in patients with LABC.[6] Although patients age $>$ 75 years have the highest incidence rates of breast carcinoma,[7] they usually

are excluded from combined modality programs because of their high rate of incidence of comorbid conditions and the widespread belief that elderly patients cannot tolerate aggressive treatments.[8,9]

Combined regimens including local treatments (surgery and radiotherapy) and hormone therapy have been suggested for more than 20 years.[10] In postmenopausal patients with LABC, the response rate to tamoxifen alone has been reported to range between 40–60%, with a duration of disease remission exceeding 36 months in some patients.[11–13]

In 1989, we designed a protocol to evaluate the use of tamoxifen in conjunction with locoregional therapies (surgery and radiotherapy) for patients with LABC who were age $>$ 75 years or who were younger but considered poor candidates for chemotherapy because of other comorbid illnesses. The objectives were to determine the antitumor efficacy of tamoxifen as preoperative therapy and to maximize breast conservation in this patient population.

MATERIALS AND METHODS

Patients were eligible to participate in the study if they were age $>$ 75 years and had: 1) T3 or T4 noninflammatory primary tumors, any N, and M0; 2) any T status, N1b ($>$ 2.5 cm), N2 or N3, and M0; or 3) any T, any N, M1 whose only metastasis was ipsilateral supraclavicular lymph node disease. Patients could have operable or inoperable LABC. Patients were seen by a multidisciplinary group of physicians, including a medical oncologist, surgeon, and radiation therapist, to confirm eligibility criteria of LABC and to select candidates for combined modality treatment, including neoadjuvant hormonal therapy. Patients age $<$ 75 years whose tumors were estrogen receptor (ER) positive and who were not good candidates for chemotherapy because of significant comorbidity (clinically determined by the investigator) also could be enrolled if the other criteria mentioned earlier were fulfilled. Concomitant invasive neoplasm was a reason for exclusion, but patients who had been treated for other malignant tumors $\geq$ 10 years before the diagnosis of breast carcinoma and who remained free of evidence of recurrence were eligible. In accordance with federal, state, and institutional policies, informed consent indicating that the patient was aware of the investigational nature of the study was obtained from all patients.

A careful history and physical examination was conducted for all patients before enrollment. Baseline studies included complete blood count, routine chemistry, tumor markers (carcinoembryonic antigen and CA 27-29), electrocardiogram, lipid profile, urinalysis, chest X-ray, bone scan, liver ultrasound or computed tomography, and bilateral mammogram. Tissue was obtained by core needle biopsy unless histologic diagnosis already was available when the patient was referred to the M. D. Anderson Cancer Center. Type, nuclear grade, and vascular and lymphatic invasion were determined by histologic analysis. ER and progesterone receptor (PR) assays, flow cytometry for DNA index, and S-phase were performed when technically possible. Patients were evaluated by a multidisciplinary group at the beginning of the study and at 3 and 6 months. Responses were documented by physical examination and imaging studies.

Preoperative therapy was comprised of 20 mg of oral tamoxifen daily for 3 months. At 3 months, all patients who had achieved a clinical complete disease remission were directed to local therapy by surgery and radiotherapy when indicated. Continuation of tamoxifen alone was allowed on a case-by-case basis. Patients with a partial response or stable disease (SD) continued the tamoxifen regimen for 3 more months, at which point response again was evaluated. Patients who had operable disease were evaluated for surgery, whereas the patients whose tumors remained inoperable were taken off the protocol and considered for chemotherapy or radiotherapy. Patients whose disease progressed at any time were removed from the protocol and offered other treatment options. The choice of breast-conserving surgery (lumpectomy) was offered to patients when surgically possible.

Radiotherapy (comprised of 50 grays (Gy) in 25 fractions to the breast and 50 Gy in 25 fractions to the internal mammary lymph nodes, axillary apex, and supraclavicular lymph node regions) was given to all patients who underwent segmental mastectomies. Patients who at the beginning of the study had axillary lymph nodes $>$ 2.5 cm or macroscopic extranodal disease received 40 Gy to the midaxilla. Patients who underwent modified radical mastectomies received radiotherapy to the chest wall, internal mammary lymph node region, and supraclavicular lymph node region if they had Stage IIIA or IIIB tumors at the time of presentation, axillary lymph node involvement at the time of surgery, regional M1 disease involving the ipsilateral supraclavicular lymph nodes at the time of presentation, and positive or close surgical margins. The chest wall and regional lymphatics were treated with the same regimen used to treat patients who underwent segmental mastectomies. Postoperatively, tamoxifen was continued at 20 mg daily for 5 years or until disease recurrence.

Overall survival (OS) was measured from the date of enrollment in the study until death or the last date of follow-up for those patients still alive. Time to progression (TTP) was measured from the first day of

TABLE 1
Patients' Characteristics

Characteristics	Patients (%)
Age (yrs)	
< 75	29 (61.7)
> 75	18 (38.3)
Race	
White	31 (66.0)
Black	12 (25.5)
Hispanic	4 (8.5)
Estrogen receptor	
Positive	38 (80.9)
Negative	4 (8.5)
Unknown	5 (10.6)
Progesterone receptor	
Positive	22 (46.8)
Negative	15 (31.9)
Unknown	10 (21.3)
Tumor stage	
II[a]	10 (21.3)
III	37 (78.7)

[a] T3N0M0.

TABLE 2
Comorbid Conditions

Condition	Age < 75 yr	Age ≥ 75 yr
Congestive heart failure	3	1
Chronic obstructive pulmonary disease	6	1
Severe diabetes mellitus	4	3
Hypertension	17	6
Cerebrovascular accidents	2	3
Coronary artery disease	2	1
Cardiac arrhythmia	4	
Valvular heart disease	2	
Others[a]	6	3

[a] One case each of inflammatory bowel disease, chronic renal failure, idiopathic thrombocytopenic purpura, cirrhosis, hypothyroidism, and Parkinson disease in the group of patients age < 75 years and one case each of Alzheimer disease, glaucoma, and debilitating arthritis in the group of patients age ≥ 75 years.

TABLE 3
Response to Tamoxifen at 3 and 6 Months, and Overall Results

Response	3 mos (n = 47)	6 mos (n = 37)	Overall
Complete response	3	0	3 (6.4)
Partial response	13	19	19 (40.4)
Stable disease	24	15	15 (31.9)
Progressive disease	7	3	10 (21.3)

treatment until the date of disease progression. Disease free survival was defined as showing no evidence of local and/or distant recurrence. Curves plotted to show the distribution of OS and TTP were calculated by the method of Kaplan and Meier,[14] and differences among distributions were tested using the log rank test.[15] The statistical significance level (*P* value) was taken as a measure of the strength of the evidence against the null hypothesis, and a probability level of 0.05 generally was considered to be statistically significant. Comparability of group outcomes was assessed by either the chi-square test or Fisher exact test.

RESULTS

Forty-seven patients participated in the study over a period of 8 years (1989–1997). Patients were followed through January 1999. Their characteristics are shown in Table 1. The median patient age at enrollment was 72 years (range, 48–86 years) and the median follow-up was 40 months (range, 5–98 months). The majority of patients (56.5%) had T4 lesions and 21.7% had T3 tumors. Two patients had synchronous bilateral breast tumors. Hormone receptor status was available for 41 patients, 90% of whom (80.4% of all patients) were found to be ER positive. The comorbid conditions are depicted in Table 2.

The efficacy results achieved with tamoxifen, with analysis at 3 and 6 months, are shown in Table 3. In summary, over the course of 6 months 3 patients (6.4%) achieved a complete response (CR), with 1 CR confirmed pathologically; 19 patients (40.4%) achieved a partial response and15 patients (31.9%) had SD. The overall clinical response rate was 47%. The two patients with bilateral breast carcinoma had the same response in both breasts. Patients with operable lesions were offered surgery; the other patients were offered other therapeutic options, additional hormonal therapy, chemotherapy, and radiotherapy.

Figure 1 summarizes the therapeutic interventions and clinical results. Forty-four of 47 patients were evaluated for surgical resection, including 10 patients who had progressive disease (PD); 6 of these 10 patients received additional treatment with chemotherapy and/or radiotherapy. Only 29 patients underwent surgery. Breast-conserving surgery was performed in 5 patients, whereas 24 patients underwent a modified radical mastectomy. The remaining 18 patients did not undergo surgery for various reasons. Nine patients were considered inoperable, three patients refused surgery, and four patients were considered poor candidates for surgery because of comorbid conditions. The other three patients were lost to follow-up after initial treatment with tamoxifen; one achieved a clinical CR but failed to return. She later developed a disease recurrence and died at age 81 years, 4 years after enrollment on the study. One patient developed PD and one had SD while receiving tamoxifen and did not return for follow-up. Radiother-

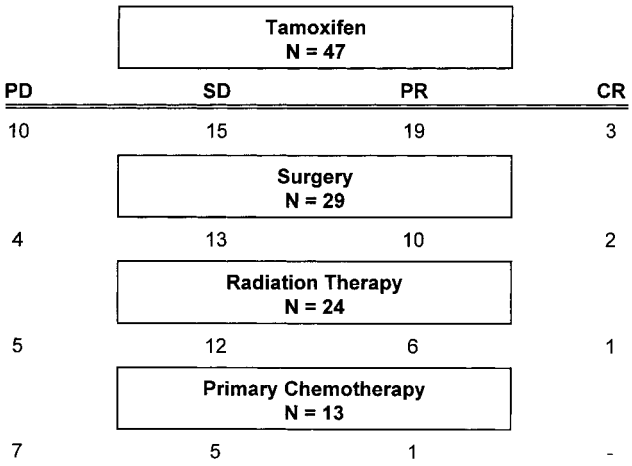

FIGURE 1. Summary of therapeutic interventions and clinical results. PD: progressive disease; SD: stable disease; PR: partial response; CR: complete response.

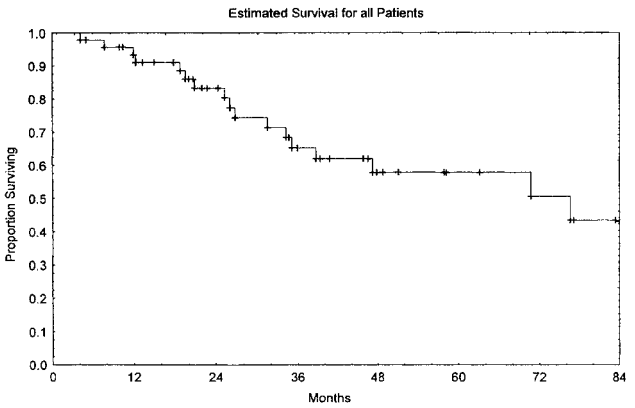

FIGURE 2. Overall survival analysis

TABLE 4
Survival Status by Response to Treatment at 6 Months

	Alive	Dead	Total
Complete response	1	2	3
Partial response	15	4	19
Stable disease	9	6	15
Progressive disease	4	6	10
Total	29	18	47

apy was given to 24 patients, including the 5 patients who underwent segmental mastectomy. Nineteen patients received radiotherapy after surgery. Two patients (one with SD and one with PD) received radiotherapy prior to surgery. Three patients had radiotherapy as the only local modality. All three previously had failed primary tamoxifen therapy and later died. Seven of the 24 patients received radiotherapy after being removed from the protocol. Thirteen patients received primary chemotherapy (Fig. 1); 1 patient initially achieved a partial response but developed PD prior to surgery.

Of the twenty-nine patients rendered free of disease by surgery, 5 patients experienced distant recurrences (1 with a local recurrence as well) and all 5 died. Four patients died of other causes (1 from ovarian carcinoma, 1 from cardiac complications, 1 from Parkinson disease, and 1 of unknown causes at age 93 years). One patient developed a contralateral breast tumor 20 months after the initial treatment, was treated with primary chemotherapy and mastectomy, and at last follow-up had been disease free for 3 years.

At last follow-up 20 patients remained free of disease (i.e., they had no local or distant recurrences). They included 14 patients who remained in the study and 6 patients who received additional treatment off the protocol and remained free of disease as well. Nine patients were alive with active disease. None of the nine patients underwent surgery. Eighteen patients had died, 14 as a result of breast carcinoma, 1 of ovarian carcinoma while free of breast carcinoma, 1 of cardiac complications, 1 of Parkinson disease, and 1 died of unrelated causes at age 93 years with no clinical evidence of breast carcinoma.

At the time of the analysis, 65% (28 of 43) of the ER positive and ER unknown patients were alive compared with only 25% (1 of 4) of the ER-negative patients (this patient was PR negative as well). Approximately 66% (21 of 32) of PR positive and PR unknown patients were alive compared with 53% (8 of 15) of the PR negative patients. Seven of these eight surviving PR negative patients were ER positive. There were 34 patients with clinically positive lymph nodes (prior to tamoxifen), 20 of whom (59%) still were alive, and 10 of the 13 patients with clinically negative lymph nodes (77%) still were alive. The median disease free survival of the 29 patients rendered free of disease was 17 months (range, 2–50 months). The median TTP among all patients was 27.5 months (range, 2–50 months). The median TTP among the clinically lymph node negative patients was 10 months (range, 1.7–31 months), and the median TTP among clinically lymph node positive patients was 5.4 months (range, 1.7–35 months). As demonstrated in Figure 2, 61% of the patients still were alive, and the median survival for this group of patients had not been reached, at the time of this analysis. Survival status by response to tamoxifen at 6 months is shown in Table 4.

Patients who experienced adverse events included one patient who developed Stage I endometrial carcinoma and underwent surgery. She was alive and free of breast and endometrial disease at the time of last follow-up. The second patient developed early endo-

metrial carcinoma 9 years after she received tamoxifen for 3 months and failed. She then received chemotherapy and at last follow-up showed no evidence of breast carcinoma. Two patients developed mild rashes and one experienced edema of the lower extremities with no deep venous thrombosis. All side effects were resolved without interruption of tamoxifen treatment, except in the case of the patient with endometrial carcinoma.

DISCUSSION

Hormonal manipulation has been used for nearly a century to treat patients with breast carcinoma.[16–18] As understanding of the natural history of breast carcinoma and the mechanism of action of agents such as tamoxifen grew, so did the need to develop new treatment schemes for frail or elderly patients who could not tolerate systemic chemotherapeutic protocols.

Tamoxifen was the result of a long search for an agent that could be used in patients whose advanced tumors were responsive to hormonal manipulation. The drug first was tested in patients with metastatic breast carcinoma in 1971.[19] It is considered an antiestrogen and acts through competitively binding to ERs, inhibiting estradiol. Tamoxifen is phase specific, tending to block cells in the G_1/G_0 phase.[20] More recently, it was found to induce apoptosis[21] of ER positive as well as ER negative cells, possibly by overexpression of c-*myc*.[22]

Widely used in treating metastatic breast carcinoma and as adjuvant treatment after surgery and chemotherapy in patients with early breast carcinoma and LABC, tamoxifen has improved survival significantly. Although the role of adjuvant therapy with tamoxifen in elderly patients with ER positive early breast carcinoma is well established, to our knowledge the role of chemotherapy or chemotherapy plus tamoxifen in patients age $>$ 65 years is unclear.[23,24] A previous study of elderly patients has shown the superiority of localized tumor excision followed by tamoxifen compared with modified radical mastectomy alone.[25] Tamoxifen also is an important agent in patients with Stage III LABC. A recent study showed that tamoxifen is more important than chemotherapy in patients with LABC.[26]

The results of our multidisciplinary regimen using tamoxifen in a neoadjuvant and postoperative setting, combined with radiotherapy and surgery, were encouraging, especially in light of the poor general condition of the patients involved. The objective response rate, close to 50%, is within the reported range of responses reported in metastatic breast carcinoma patients with heterogeneous hormone receptor status.[27] The overall survival was very good, with the patients having yet to reach their median survival at the time of last follow-up. Nearly 20% of the surgical cases involved breast conservation procedures, a percentage that could have been higher if some patients had not chosen radical procedures despite the fact that technically their breasts could have been preserved. The overall objective, clinical, and pathologic response rates are lower than those noted with primary anthracycline-containing chemotherapy.[4,5,28,29] However, we cannot compare these therapeutic modalities because this was not a randomized study comparing primary hormonal therapy and primary chemotherapy and, moreover, patients included in this trial routinely are excluded in chemotherapy trials. We also cannot recommend one therapy over the other as the best initial therapeutic choice. However, we do believe this choice adds to the therapeutic armamentarium in the management of patients with LABC.

Analysis of prognostic variables suggested that important prognostic factors were the tumor's hormonal receptor status and the number of positive axillary lymph nodes at the time of surgery. However, the sample size was too small for the results of the Fisher exact test to reach statistical significance. Although the number of patients with hormone negative tumors was small, their shorter survival showed their response to antiestrogen therapy to be clearly inferior, consistent with previous reports concerning patients with metastatic breast carcinoma.[30] A few patients with hormone receptor negative breast carcinoma may respond to tamoxifen, but the majority of patients should be considered for alternative methods of treatment. We also detected a trend toward better outcome in patients with fewer than three positive lymph nodes at the time of surgery, again consistent with previous studies that have shown that the lymph node status at the time of surgery is the best prognostic factor in women with LABC treated with primary systemic chemotherapy.[4–28] Unfortunately the small number of patients precluded us from further subgroup analysis. Patients who responded to 3 months of preoperative tamoxifen fared better than those who did not, but objective response at 6 months did not correlate with statistically significant improved outcome. The initial stage of disease had no significant impact on OS or TTP. In contrast to the approximately 10–15% pathologic CR observed in LABC patients treated with chemotherapy,[4,28,29] only 1 patient (2.1%) achieved such a response in the current study. She was alive with no evidence of recurrence at the time of last follow-up. It is reasonable to postulate that patients with pathologic CR achieved with hormonal agents may have longer TTP and OS.

Other clinical trials have documented the activity of primary hormonal therapy (neoadjuvant), tamoxifen, and other hormonal agents, such as letrozole, in patients with breast carcer.[11–13,31] Tamoxifen produced an objective response rate of 40–60% in patients treated with primary hormonal therapy. The efficacy of letrozole given as primary systemic therapy was determined in a small study in patients with ER positive LABC or large operable breast tumors. Twenty-four patients were treated with letrozole (12 patients with a dose of 2.5 mg and 12 with a dose of 10 mg). Patients were assessed by monthly ultrasound and changes in tumor volume over a 3-month period were calculated. The median percentage reduction in tumor volume with letrozole was 81%. There was one complete pathologic response, and three patients had residual microscopic tumor foci only at the time of definitive surgery. The investigators compared these results with those obtained in their previous series of 65 patients treated using an identical protocol with tamoxifen, in which the median percentage reduction in tumor volume was 48%.[31]

The low rate of incidence of severe side effects also deserves attention. However, the median duration of tamoxifen administration was relatively short and the follow-up period also was short. One patient developed tamoxifen-related endometrial carcinoma. No patient developed thrombosis while receiving tamoxifen, and no patient discontinued the drug due to side effects.

The results of the current study show that in elderly patients or in patients with poor performance status due to concomitant diseases tamoxifen is feasible as neoadjuvant therapy and is a reasonable alternative to traditional, more aggressive, cytotoxic preoperative therapy. The results observed in the select group of patients in the current study were very encouraging and a larger study is warranted.

The benefits of this approach included good tolerance with a low side effect profile, low cost, and reasonable outcome, with some patients able to be treated with breast-preserving surgical resection instead of mastectomy. We do not recommend this approach for patients with ER negative tumors. There were neither unexpected adverse events nor a higher incidence rate of adverse events.

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