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Fifteen-year median follow-up results after neoadjuvant doxorubicin, followed by mastectomy, followed by adjuvant cyclophosphamide, methotrexate, and fluorouracil (CMF) followed by radiation for stage III breast cancer: a phase II trial (CALGB 8944)

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Abstract

Purpose—To describe long-term results of a multimodality strategy for stage III breast cancer utilizing neoadjuvant doxorubicin followed by mastectomy, CMF, and radiotherapy.

Patients and methods—Women with biopsy-proven, clinical stage III breast cancer and adequate organ function were eligible. Neoadjuvant doxorubicin (30 mg/m² days 1–3, every 28 days for 4 cycles) was followed by mastectomy, in stable or responding patients. Sixteen weeks of postoperative CMF followed (continuous oral cyclophosphamide (2 mg/kg/day); methotrexate (0.7 mg/kg IV) and fluorouracil (12 mg/kg IV) weekly, weeks 1–8, and then biweekly, weeks 9–16). Radiation therapy followed adjuvant chemotherapy.

Results—Clinical response rate was 71% (79/111, 95% CI = 62–79%), with 19% complete clinical response. Pathologic complete response was 5% (95% CI = 2–11%). Median follow-up is 15.6 years. Half of the patients progressed by 2.2 years; half died by 5.4 years (range 6 months–15 years). The hazard of dying was greatest in the first 5 years after diagnosis and declined thereafter. Time to progression and overall survival were predicted by number of pathologically involved lymph nodes (TTP: HR [10 vs. 1 node] 2.40, 95% CI = 1.63–3.53, $P < 0.0001$; OS: HR 2.50, 95% CI = 1.74–3.58, $P < 0.0001$).

Conclusions—After multimodality treatment for locally advanced breast cancer, long-term survival was correlated with the number of pathologically positive lymph nodes, but not to clinical response. The hazard of death was highest during the first 5 years after diagnosis and declined thereafter, indicating a possible intermediate endpoint for future trials of neoadjuvant treatment.

Keywords

Breast cancer; Chemotherapy; Locally advanced; Long-term follow-up; Neoadjuvant; Stage III

Introduction

Neoadjuvant chemotherapy is a standard treatment for stage III breast cancer. It allows direct evaluation of the tumor's sensitivity to chemotherapy and the possibility of breast conserving therapy in women who might otherwise need a mastectomy. Yet, local and distant relapse and mortality rates are high with stage III breast cancer. Doxorubicin-based combination chemotherapies have high response rates when used in the neoadjuvant setting, with overall response rates of 78–95% and clinical complete response rates of 8–49% [1–7]. Nevertheless, local relapses are seen in over 35% of patients treated with chemotherapy followed by either radiation or surgery [1, 2]. The use of chemotherapy improves disease-free and overall survival, but the optimum combination of drugs, dose, and schedule remain undefined. Prior to the initiation of this study, the CALGB had conducted a trial which treated women with CAFVP followed by a randomization to surgery or radiation therapy (CALGB 7784) [1].

The current trial was developed to build upon prior results in treatment of stage III breast cancer and to establish a model to which high-dose alkylator or other innovative therapies could be added in sequence. The dose and schedule of doxorubicin were adopted from a pilot study performed by Jones et al. [8], in which response rates compared favorably to

those reported for conventional doxorubicin-based combination chemotherapies for metastatic breast cancer [9] and are very similar to those reported by Hortobagyi et al. using maximally tolerated inpatient CAF [10].

Following four cycles of doxorubicin-based treatment, patients had definitive surgery (modified radical mastectomy or radical mastectomy). Based on the Milan data demonstrating a beneficial outcome for sequential doxorubicin followed by CMF, they then received four months of continuous CMF, followed by radiation therapy [11]. We chose to use this combined local modality (i.e. surgery and radiation) approach because of the high local recurrence rates noted on CALGB 7784 with either modality alone [1].

Now, at a median follow-up of 15.6 years, this report describes the results of our phase II trial in terms of incidence of clinical response to preoperative doxorubicin, time to first disease progression and overall survival after this multimodality regimen for stage III breast cancer. We also describe toxicity of the chemotherapy regimens and examine pretreatment and neoadjuvant response variables as they relate to long-term events. Though the regimen described was designed almost 20 years ago and is not typical of current options, the very prolonged follow-up available for this non-randomized, prospective trial allow us an unusual opportunity to explore the associations between tumor presentation, response, and long-term outcomes.

Patients and methods

Eligibility criteria included pathologically documented clinical stage III adenocarcinoma of the breast (T_XN_2 , T_3N_{1-2} , T_4N_X , without distant metastases) (Reference Manual for Staging of Cancer, Third Edition, American Joint Committee on Cancer, 1988). Bilateral mammograms, CT scan of the chest, and bone scan were required for all patients. Measurable or evaluable disease was accepted. Measurable disease was defined as any clearly defined mass or lymph node measuring ≥ 2 cm on physical examination, sonography, CT scan, or mammogram. Evaluable disease was any poorly circumscribed mass or inflammatory cancer that could not be reproducibly measured on physical examination, sonography, CT scan, or mammogram. Patients with synchronous and bilateral primary cancers were excluded. Patients were excluded if they had previous or concomitant malignancy, except inactive non-melanoma skin cancer, in situ carcinoma of the cervix or other non-breast cancer if the patient has been disease-free for ≥ 10 years. All patients required evaluation by a surgeon and radiotherapist prior to study entry. No prior therapy other than a biopsy was allowed. Patients were required to have an expected survival of >6 months, a Zubrod performance status of 0–1, normal hematologic, renal, hepatic and cardiac (by LVEF) function. All patients gave written Institutional Review Board approved informed consent. Patients with a history of other significant serious medical or psychiatric illness considered likely to compromise their ability to withstand intensive therapy, or those with specific history of congestive heart failure, myocardial infarction, or symptomatic cardiac arrhythmias were excluded, as were patients with chronic liver disease.

The tumor was reassessed by clinical exam before each cycle of neoadjuvant chemotherapy. Restaging was required by mammogram before surgery, by bone scan before radiation, and by bone scan and chest X-ray every 6 months after treatment.

The induction schedule was modified from Jones et al. [9]. Treatment was based on actual weight and height. Neoadjuvant chemotherapy with doxorubicin was given on a 28-day schedule for responding patients. The starting dose of neoadjuvant doxorubicin was 30 mg/m² IV bolus on days 1, 2, and 3, given at the same time each day. Dose modification was made based on treatment tolerance. Dose escalation was provided for doxorubicin in subsequent cycles as follows: patients who did not experience dose-limiting toxicity (defined as neutropenia and fever requiring hospitalization, a platelet count nadir of 40,000, a platelet or red cell transfusion requirement, or any Grade 3 or 4 non-hematologic toxicity) received an increased dose at increments of 5 mg/m² with each successive cycle to a maximum of 40 mg/m²/day for three days. Subsequent cycles were delayed if the granulocyte count was 1,500 or the platelet count 100,000 on the scheduled first day of treatment. Doses of doxorubicin were decreased by 5 mg/m²/day if any of the following occurred: nadir neutropenia of 500 granulocytes/ml for more than seven days; hospitalization for neutropenic fever; thrombocytopenia of 50,000/ml for seven days; platelet or red cell transfusion; or any Grade 3 or 4 non-hematologic toxicity. Doxorubicin was discontinued in patients who developed new symptomatic arrhythmias, symptomatic congestive heart failure, or a decline in the left ventricular ejection fraction of 15% from the pretreatment value or to below the lower limit of normal. Patients were examined monthly and removed from study treatment at the first evidence of tumor progression or if there was no improvement after two cycles of therapy.

After completion of the doxorubicin induction chemotherapy, patients were reevaluated for surgery. Either a radical or modified radical mastectomy was allowed at the discretion of the operating surgeon. Tumor fixation to the chest wall, involvement of the skin over an area too wide to be excised, or fixed regional lymph nodes which could not be completely excised were considered indications of inoperability.

Patients then received CMF for 16 weeks beginning 14–21 days after surgery. A modification of the original Cooper regimen was used: cyclophosphamide 2 mg/kg/day orally continuously for 16 weeks; methotrexate 0.7 mg/kg/week IV and 5-fluorouracil 12 mg/kg/week IV, both for eight consecutive weeks, and then biweekly until week 16. On the day of scheduled administration of drugs, if neutrophil count was 1,800 and platelet count was >100,000/μl, full doses were given. If neutrophil count was 1,500–1,799 and platelet count was >100,000/μl, doses of all drugs were decreased by 25%. If neutrophil count was 1,499–1,200 or platelet count was 75,000–100,000/μl, doses of all drugs were reduced by 50%. If neutrophil count was 1,200 or platelet count was <75,000/μl, chemotherapy was held. Doses of methotrexate were adjusted based on hepatic and renal function; full doses were given if bilirubin was <1.5 mg/dl, SGOT/SGPT were <100 IU, and creatinine was <1.6 mg/dl; 50% dose was given if bilirubin was 1.5–3 mg/dl, SGOT/SGPT were 100–250 IU, or creatinine was 1.6–1.9 mg/dl; dose was held if bilirubin was >3 mg/dl, SGOT/SGPT were >250 IU, and creatinine was >2.0 mg/dl. Methotrexate and fluorouracil were held if stomatitis or diarrhea was evident on the day of administration. Cyclophosphamide was not

given to any patient with hematuria. When hematuria subsided, chlorambucil was substituted for cyclophosphamide at a dose of 2 mg for each 50 mg of cyclophosphamide. Doses that were delayed or omitted were not made up. Patients with estrogen receptor (ER) positive tumors received tamoxifen 10 mg twice a day for five years.

After recovering from chemotherapy toxicities, radiotherapy was administered; CT scans obtained at initial diagnosis were used to assist in planning treatment volumes. Three specific techniques were defined. The total treatment dose and fractionation to the prescribed points were 5,040 cGy in 28 fractions of 180 cGy to supraclavicular nodes, chest wall, and internal mammary nodes, and axillary nodes. If a boost was selected to the chest wall, an additional 1,504 cGy in eight fractions of 188 cGy was provided, bringing the total dose to the boosted site to 6,544 cGy in 36 fractions. A similar dose was given to the internal mammary nodes in selected patients.

Statistical methods

The primary endpoint of this study, upon which statistical power was computed, was the incidence of clinical response to neoadjuvant doxorubicin. Clinical response was defined as a complete or partial tumor response. A complete clinical response required the disappearance of all evidence of cancer based on physical examination for four weeks or until surgery. A partial clinical response required a decrease in the product of the perpendicular diameters of the tumor on physical exam by 50% lasting for four weeks or until surgery. Incidence of pathologic complete response (pCR) was the percentage of patients with no evidence of tumor in the resected mastectomy specimen and no involved lymph nodes at surgery. The 95% confidence intervals around clinical and pathologic response incidence used exact binomial methods. Time to first disease progression was defined as the interval from study entry until date of first documented disease spread, whether local, distant or both synchronously, or death without disease spread. Surviving patients without disease spread were censored at the date last known to be progression-free. Overall survival was the interval from study entry until date of death due to any cause. Surviving patients were censored at the date last known to be alive. Time-to-event distributions were estimated using the Kaplan–Meier product limit method [12].

Cox proportional hazards regression was used to assess the relationship of several variables obtained both at pre-treatment (patient demographics, clinical tumor characteristics) and at mastectomy (number of pathologically determined involved nodes and clinical response to induction therapy) with OS and time to progression [13]. In the latter case, the landmark method [14] was used in which OS and TTP were calculated starting at the landmark of 4 months after study entry. Four months was chosen as the landmark because it coincided with both the assessment of clinical tumor response to doxorubicin and mastectomy. Covariables were assessed using the Wald chi-square statistic.

Toxicity type and severity of toxicity were defined according to the CALGB Expanded Common Toxicity Criteria. Toxicity was tabulated per patient as the worst severity by type and reported separately for the intervals during doxorubicin and CMF therapies.

The CALGB Statistical Center managed patient registration and data collection. Data were reviewed by the study chairperson and the Data Audit Committee. CALGB statisticians performed all statistical analyses using SAS 9.1 (SAS Institute, Cary, NC) on data in the CALGB database as of June 2007.

Results

Between June of 1990 and January of 1992, 113 women with Stage III breast cancer were enrolled. Patient characteristics are shown in Table 1. Fifty-two percent were under 50 years of age at diagnosis, 23% were over the age of 60, and 8% over the age of 70. Tumors were estrogen-receptor negative in 57% and progesterone-receptor negative in 64%. Disease was measurable in 98 (87%) patients. Tumors were <2 cm in 11 (10%), between 2 and 5 cm in 12 (11%), and >5 cm in 84 (74%). Axillary nodes were clinically apparent in 73% of patients. Five patients, all with measurable lesions, were ineligible, as follows: wrong stage (2), missing required tests/documentation (2) and began treatment too soon (1).

Nearly half of patients (55, 49%) had tumors that were hormone receptor-negative, defined as both estrogen and progesterone receptor negative; 43% of patients had hormone receptor-positive tumors, defined as estrogen and/or progesterone receptor positive. Of the total sample, 104 patients had available data for both hormone receptor status and tamoxifen use. Tamoxifen was given to 32 (65%) of the 49 women with hormone receptor positive disease and 8 (15%) of 55 women with hormone receptor negative disease.

Induction doxorubicin

All 113 registered patients began preoperative doxorubicin. Two patients could not be assessed for response to induction therapy due to missing repeat tumor assessments, which left 111 patients. Twenty-six (26) patients had stable disease at the end of two cycles. After four cycles of doxorubicin, clinical responses were as follows: complete 21/111 (19%); partial 58/111 (52%); stable 21/111 (19%); and progression 11/111 (10%). The overall clinical response rate (CR + PR) was 71% (95% CI of 62–79%). Table 2 shows the observed effect of various patient and pretreatment variables on tumor response to neoadjuvant doxorubicin. Larger tumor size ($P=0.042$) related to tumor response, while the presence of palpable lymph nodes was of marginal significance ($P=0.052$). With an OR of 2.14, the odds of responding to neoadjuvant doxorubicin were more than double for patients with tumors larger than 5 cm compared to tumors between 2 and 5 cm; similarly, patients whose tumors were 2–5 cm were twice as likely to respond as tumors up to 2 cm. Compared to patients without palpable lymph nodes, the odds of responding to doxorubicin were about two and three quarters larger for those with clinically apparent nodes (OR = 2.77).

Toxicity of neoadjuvant doxorubicin is presented in Table 3. There were no lethal toxicities during induction therapy. However, there was one possible treatment-related death, which occurred 15 months after enrollment. This was a 78-year-old patient with inflammatory disease who died from congestive heart failure. The most frequent severe (Grade 3) and life-threatening (Grade 4) toxicities were hematologic (granulocytopenia, 90%; neutropenia, 81%; lymphopenia, 38%; thrombocytopenia, 37%; and anemia, 17%) and gastrointestinal (stomatitis, 42%; esophagitis, 12%; nausea, 8%; and vomiting, 7%). In addition, there was

one report each of Grade 4 dyspnea and mood, and 14 (13%) patients with Grade 3–4 infection. Only two patients reported any severe cardiac side effects during induction therapy; both were related to decline in cardiac function.

Surgery

Of the 113 patients enrolled, eleven patients had disease progression while on induction therapy and, of these, six patients were unable to have protocol-directed surgery as a result of disease progression. The remaining 107 patients underwent mastectomy and their specimens were examined for the presence of residual tumor. Complete information from operative reports was available for 102 of the 107 mastectomy patients (Table 4). Five of these 102 patients (5%; 95% CI: 2–11%) had pCR with no tumor noted in the resected specimen and negative axillary lymph nodes. Nineteen patients had residual tumor in the mastectomy specimen but negative lymph nodes and 3 had no residual tumor in the breast, but positive lymph nodes. Pathologic nodal status by clinical response to preoperative doxorubicin is shown in Table 5. Out of 77 patients whose tumors clinically responded to neoadjuvant doxorubicin, only 5 (6%) had pCRs. All 24 tumors that did not respond clinically had pathologic evidence of disease.

Adjuvant CMF

Toxicity of adjuvant CMF is presented in Table 6; it was generally well-tolerated. The most common Grades 3 and 4 adverse events were hematologic, namely, WBC (54%), platelets (7%), granulocytes (56%) and lymphocytes (46%). There was one report each of life-threatening (Grade 4) hemoglobin, platelets, dysrhythmias and partial thromboplastin time. The most common non-hematologic toxicity of Grade 3 or higher severity was stomatitis (6%). All other reported toxicities of Grade 3 or 4 occurred in fewer than 6% of patients. Gastrointestinal discomfort was typically moderate (Grade 2). There were two cases of hematuria, which were both moderate (Grade 2).

Overall survival

At time of reporting, the median follow-up was 15.6 years. Figure 1 shows the Kaplan–Meier estimates of overall survival (OS) and time to first disease progression (TTP) for the 113 study entrants. The median survival was 5.4 years with 57 patients surviving at least 5 years, 36 patients surviving at least 10 years and 25 surviving at least 12 years.

Standard multivariate proportional hazards modeling indicated that only performance score related with OS, and only mildly ($P = 0.069$). Compared to patients with a performance score of 0, patients with a performance score of 1 had a hazard of dying which was 1.71 times greater. After controlling for performance score, no other variables were of statistical significance.

Results of multivariate proportional hazards landmark analyses indicated that the number of pathologic positive nodes was highly predictive of OS ($P < 0.0001$). For instance, patients with 10 positive nodes had a hazard of dying that was two and a half times that of patients with only one positive node (hazard ratio = 2.50, 95% CI of 1.74–3.58). Clinical response to neoadjuvant therapy did not predict OS.

We also assessed survival by hormone receptor status (ER and/or PR-positive defined hormone receptor positive) and by whether or not adjuvant tamoxifen therapy was given (Fig. 2). Median survival was 7.7 years for patients with receptor positive breast cancer who received tamoxifen and 3.7 years for receptor negative breast cancer not treated with tamoxifen ($P = 0.024$). For patients with receptor positive tumors who did not receive tamoxifen, median survival was 2.4 years.

The overall hazard of dying was highest within the first 5 years after beginning protocol therapy, reaching the maximum hazard of 20% at 2 years, and generally declined thereafter (Fig. 3). The increase in hazard at years 8 and 14 is likely due to large variation in a decreasing number of patients at risk. The role of both tumoral hormone receptor status and tamoxifen related to the hazard of dying is as follows. For patients with hormone receptor positive tumors, the hazard of dying was highest within the first 4–6 years after beginning protocol treatment; the maximum hazard within this interval occurred at 3 years. The hazard of death at 3 years was 50% for those patients who did not receive tamoxifen compared to 18% for those who did. Thus, the addition of tamoxifen was associated with a 64% decrease in the hazard of dying for patients with hormone receptor positive disease. The hazard of dying for patients with hormone receptor negative tumors was about midway between the two-receptor positive groups (See Fig. 4).

Time to first disease progression

The median time to first progression was just over 2 years (Fig. 1). At last contact, 27 patients were alive and free from progressive disease in any site. Of the 86 patients with events, disease spread accounted for 94% of events, specifically, to local site(s) alone (27%), to local and distant sites synchronously (22%) and to distant site(s) alone (45%). The remaining 6% of events resulted from patients who died from non-breast-cancer causes prior to any disease relapse.

Of the 81 patients whose disease progressed locally and/or distantly, half experienced disease spread to only one site, while one-third experienced metastases to two sites.

Results of standard multivariate proportional hazards modeling showed that no pretreatment variables were significantly related to TTP. As with OS, landmark analyses showed that the number of pathologically positive nodes was the only variable highly predictive of TTP ($P < 0.0001$). For instance, patients with 10 positive nodes had a hazard of progressing that was more than twice that of patients with only one positive node (hazard ratio = 2.40, 95% CI of 1.63–3.53). Clinical response to neoadjuvant therapy did not predict TTP.

New primaries

Seven patients were diagnosed with new primaries between 3 and 10 years after beginning protocol therapy. Second primary cancers included the following: pancreas (1), breast (2), basal cell (1), ovary (1), rectum (1) and MDS (1). This last patient developed myelodysplastic syndrome 9.7 years from study entry and is still alive 3.5 years later.

Discussion

This phase II trial of neoadjuvant therapy, with its extended follow-up, provides prospectively collected data with which to explore long-term outcomes in women with clinical stage III breast cancer. The median survival in this group was 5.4 years and 25 (22%) women survived at least 12 years, demonstrating the great heterogeneity of this disease with respect to lethality. In predicting overall survival, baseline performance status and number of pathologically involved nodes were the only significant predictors. We also looked at long-term outcome, for which hormone receptor status was predictive, such that having no recurrence in 5 years was a much stronger predictor of long-term outcome in patients whose tumors were hormone receptor negative than in patients whose tumors were hormone receptor positive.

With regard to the neoadjuvant component of this study, we observed a clinical response rate to doxorubicin of 71%, with a clinical complete response rate of 19%, but a pCR rate of only 5%. Of note, for our study, pCR was defined as “no evidence of tumor in the resected specimen”. We do not know if there were cases in which there was residual ductal carcinoma in situ without invasion. Based on the results of other studies, however, we think it is very likely that there were such patients, and, had they been counted in the pCR group, the rate of pCR would have been higher. Nonetheless, our findings are similar to reports from other trials, where high clinical response rates were seen but pCR rates were disappointing [15–21]. This trial was designed over twenty years ago, and it is possible that newer regimes are more effective. The addition of taxanes to anthracyclines, for instance, has been shown to improve response rates in metastatic disease and to add benefit in the treatment of early stage disease such that taxane–anthracycline combination regimens are now considered standard in the adjuvant and neoadjuvant setting [22–24]. Schedules with shorter intervals between doses of chemotherapy, so-called dose-dense, are also more effective [25].

Today, neoadjuvant therapy for breast cancer is gaining acceptance in practice for its ability to observe the tumor’s response to treatment and gain in vivo information about breast cancer biology. In-breast responses can increase the rate of breast conservation and possibly provide prognostic information. In this study, worse overall survival was associated with poor baseline performance status and higher number of involved nodes at surgery, paralleling results of other reports [18, 21, 26–28]. However, in distinction to other recent reports, clinical response to neoadjuvant doxorubicin did not predict long-term survival.

The assumption that response to neoadjuvant therapy implies a better overall outcome is one that is important to ongoing clinical trials in which neoadjuvant therapy is employed for much lower stage disease than the patients in our study [16, 26, 29, 30]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) study B27, comparing docetaxel following doxorubicin and cyclophosphamide (AC-docetaxel) compared to doxorubicin and cyclophosphamide (AC) alone, included patients with much lower disease burden than our study, in that women with stage I breast cancer were eligible, and also differed from our study in the definition of pCR, which was the absence of invasive disease (in situ disease without invasion was considered pCR) [31]. As a result, very high pCR rates were seen.

Clinical response and complete response rates to four cycles of preoperative AC were 85 and 40%, respectively; the addition of four cycles of preoperative docetaxel increased those rates to 91 and 64%, respectively [32]. At surgery, pCR rates for AC and AC-docetaxel were 14 and 26% in the breast ($P < .001$) and 51 and 58.2% in the axillary nodes ($P < .001$). Despite a doubling of the pCR rate with the addition of docetaxel to AC, there was no survival difference between the treatment groups at a median follow-up of 77.9 months, though patients who had a better response generally had longer disease-free survival and overall survival. This is consistent with our observation that issues beyond response are important.

In other studies of neoadjuvant chemotherapy for locally advanced breast cancer, high tumor grade and ER-negativity predicted response to preoperative chemotherapy and, usually, overall outcome [16, 31–39]. For instance, in a retrospective analysis of 1,731 patients from MD Anderson Cancer Center with stage I–III non-inflammatory breast cancer treated with primary chemotherapy, hormone receptor status predicted pCR and long-term outcome [40]. Pathologic CR occurred more frequently in hormone receptor negative tumors (24 vs. 8%, $P < 0.001$) and was a significant predictor of survival—regardless of HR status. With and without pCR, reported 5-year overall survival rates were 96.4 and 84.5% ($P = 0.04$) for patients with HR+ tumors and 83.9 and 67.4% ($P = 0.003$) for patients with HR-negative tumors. After adjustment for adjuvant hormonal therapy, HR status, clinical stage, and nuclear grade, patients with pCR had 0.36 times the risk of death. In a retrospective study of 399 patients with large or locally advanced breast cancer treated at the European Institute of Oncology, pCR rates were higher in ER-negative tumors, but this did not translate into better survival [37]. In ER-negative versus ER-positive tumors, the pCR rates were 33 and 7.5% and the rates of node-negative status at surgery were 42.9 and 21.7%, respectively, but four-year disease-free survival was worse in patients with ER-negative disease (41 vs. 74%, $P < 0.0001$). Ring et al. from the Royal Marsden Hospital, performed a retrospective review of 435 patients receiving neoadjuvant chemotherapy, and found that pathologic response did not have prognostic significance in patients with ER-positive tumors [41]. The pCR rate in their study was 12% overall—but less frequent in ER+ than in ER-negative tumors (21.6 vs. 8.1%, $P < 0.001$). Pathologic CR translated into better overall survival for the ER-negative subset ($n = 111$, 5 year overall survival 90 vs. 52%, $P = 0.005$) but not for the ER positive subset ($n = 271$, 5 years overall survival 93 vs. 79%, $P = 0.3$). Furthermore, they concluded that prognosis was similar in ER-positive tumors and ER-negative tumors who had achieved pCR. It is important, therefore, that results of neoadjuvant studies be presented in terms of hormone receptor status because inclusion of patients with estrogen receptor-positive cancers may attenuate results. Rather than ‘lumping’ all patients, regardless of hormone receptor status, we should probably be ‘splitting’ and treat patients based on hormone receptor status of the tumor.

Long-term follow-up of 15.6 years in this study affords us the ability to examine other issues beyond response and median survival. Nineteen of the original 113 patients were alive at more than 13 years of follow-up. Half of these patients with clinical stage III breast cancer experienced progression by 2.2 years and half had died by 5.4 years. These figures are remarkably similar to those from other reports, even though the baseline staging workup was relatively limited [27, 42, 43]. Overall, the hazard of dying was highest in the first 5 years

after diagnosis and we found that hormone receptor status was predictive of outcome: having no recurrence in the first 5 years was a much stronger predictor of long-term outcome in patients whose tumors were hormone receptor negative than in patients whose tumors were hormone receptor positive. An analysis of trial data from the Cancer and Leukemia Group B and the US Breast Cancer Intergroup, also supports the good prognosis of persons surviving beyond 5 years and the relationship of hormone receptor status to response to therapy [44]. In that analysis, patients who had hormone receptor negative tumors had better rates of response to chemotherapy and the risk of recurrent breast cancer was highest in the first three years of follow-up. After 3–5 years, it was only 2–4% per year and was not influenced by treatment, nodal status, or tumor size. These investigators propose that cancers that have not recurred by 3–5 years after diagnosis are less aggressive or are sensitive to, and therefore effectively treated by, systemic therapy and that lack of recurrence after the first couple of years is a more important prognosticator than are baseline clinical characteristics.

The main strengths of this report is its prospective, phase II, multicenter design and its long-term follow-up. Limitations include its the small sample size which limits the power to find significant results in subset analyses. Second, the study was started in 1989, when treatment options and tumor assays were less available. The chemotherapy approach is outdated, as taxanes are now a standard part of neoadjuvant treatment regimens. Factors now known to be important prognostic and predictive factors in treatment of breast cancer, such as HER2, were not collected and are not available in the dataset for analyses. Thirdly, as with all clinical trials, the results may not be representative of those seen in the general population of breast cancer patients who are not treated on clinical trials. Lastly, tamoxifen was prescribed to patients whose tumors were ER positive, but not to patients whose tumors were ER-negative and PR-positive, which accounted for about 1/3 of the women with hormone receptor positive tumors.

In summary, the prolonged follow-up for this moderate-sized, phase II trial provides an exceptional opportunity to study factors that predict long-term outcome. First, the number of pathologically involved nodes, but not the pathologic response in the breast, was predictive of survival. This is important because the neoadjuvant setting is considered an ideal model for studying chemosensitivity in vivo [45]. Hence if the tumor's chemosensitivity does not directly correlate with survival caution must be exercised in bringing seemingly successful neoadjuvant regimens into the adjuvant setting. Second, we found an expected interaction between hormone receptor status and use of adjuvant tamoxifen in terms of survival, such that patients with hormone receptor positive tumors who were treated with tamoxifen had better outcome. From this, we suggest that future trials of neoadjuvant treatment examine outcome separately for patients with tumors that are hormone receptor negative and positive. High pCR rates in nonrandomized trials and differences in pCR rates between treatments in randomized neoadjuvant trials might be explained by high proportions of ER-negative patients and imbalances in ER status between treatment arms, respectively. Finally, we find that the hazard of death declines for patients surviving past 5 years after diagnosis, suggesting an alternate intermediate endpoint of 5-year survival for future trials of neoadjuvant therapy. The biologic explanation for this observation should be explored.

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Number of Patients at Risk

OS	113	86	59	53	42	36	25	8	0
TTP	113	58	44	39	32	20	13	1	0

Fig. 1.

Overall survival and time to progression for all patients

Number of Patients at Risk									
HR+, +Tam	32	32	25	22	16	15	10	4	0
HR+, -Tam	17	11	4	3	2	1	0	0	0
HR-	55	35	25	23	19	16	11	3	0

Fig. 2.

Overall survival by hormone receptor (HR) status and use of adjuvant tamoxifen

Fig. 3.
Hazard of dying for all patients

Fig. 4.
Hazard of dying by hormone receptor status and use of adjuvant tamoxifen

Table 1

Patient and disease characteristics at study entry

Characteristic	N (%)
Total	113 (100)
Age at study entry	
<40	19 (17)
40–49	39 (35)
50–59	29 (26)
60–69	17 (15)
70+	9 (8)
Race	
White	92 (81)
Black	16 (14)
Other	5 (5)
Menopausal status	
Premenopausal	51 (45)
Postmenopausal	62 (55)
ER status	
Negative	64 (57)
Positive	43 (38)
Missing	6 (5)
PR status	
Negative	73 (64)
Positive	28 (25)
Missing	12 (11)
Hormone receptor status	
Negative (both ER and PR)	55 (49)
Positive (ER and/or PR)	49 (43)
Missing	9 (8)
Performance score	
0	100 (88)
1	12 (11)
2	1 (<1)
Tumor evaluation	
Measurable	98 (87)
Evaluable	15 (13)
Tumor size (by physical examination)	
<2 cm	11 (10)
2–5 cm	12 (11)
>5 cm	84 (74)
unknown	6 (5)
Inflammatory disease	

Characteristic	N (%)
No	37 (33)
Yes	74 (65)
Unknown	2 (2)
Nodal status	
Not palpable (N0)	30 (27)
Palpable (N1)	82 (73)
Unknown	1 (<1)

Table 2

Multivariate analysis of clinical response to neoadjuvant doxorubicin by patient and pre-surgery tumor characteristics

Variable	More:less Likely to respond	Odds ratio	95% confidence interval around OR	P-value
Palpable lymph nodes	Yes:No	2.77	0.99–7.72	0.052
Tumor size (by PE)	>5:2–5 cm 2–5: 2 cm	2.14 ^a	1.03–4.45	0.042
Inflammatory disease	No:Yes	2.23	0.74–6.71	0.15
Age at enrollment	50: <50	1.54	0.34–7.02	0.58
Patient race	Nonwhite:White	1.23	0.36–4.22	0.75
Menopausal status	Pre:Post	1.83	0.43–7.86	0.42
Hormone receptor status	Positive:Negative	1.72	0.64–4.66	0.28
Performance score	0:1	1.91	0.44–8.26	0.39

^aOR comparison of: (a) >5 vs. 2–5 cm and (b) 2–5 vs. 2 cm

Table 3

Grades 2–4 selected toxicities reported during neoadjuvant doxorubicin

Toxicity type	Grade of toxicity			N with data N
	2 (Moderate) N (%)	3 (Severe) N (%)	4 (Life Thr) N (%)	
Hematologic				
WBC	17 (15)	53 (50)	34 (31)	111
Platelets	10 (9)	30 (27)	11 (10)	111
Hemoglobin	45 (41)	17 (15)	2 (2)	111
Granulocytes	2 (2)	14 (13)	85 (77)	111
Lymphocytes	21 (19)	29 (27)	12 (11)	109
Cardiac				
Dysrhythmias	1 (1)	0 (0)	0 (0)	105
Cardiac function	9 (8)	1 (1)	0 (0)	106
Ischemia	0 (0)	0 (0)	0 (0)	104
Pericardial	0 (0)	0 (0)	0 (0)	105
Other cardiac	0 (0)	1 (1)	0 (0)	100
Other				
Infection	19 (17)	13 (12)	1 (1)	110
Fever w/o infection	15 (14)	0 (0)	0 (0)	109
Nausea	26 (23)	9 (8)	0 (0)	111
Vomiting	25 (23)	7 (6)	1 (1)	111
Diarrhea	12 (11)	1 (1)	0 (0)	110
Stomatitis	24 (22)	41 (37)	5 (5)	111
Esophagitis/dysphagia	7 (6)	12 (11)	1 (1)	110
Other mucosal	5 (5)	3 (3)	0 (0)	104
Hematuria	0 (0)	0 (0)	0 (0)	107
Anorexia	18 (16)	4 (4)	0 (0)	110
Skin	8 (7)	2 (2)	1 (1)	111
Pain	7 (6)	3 (3)	0 (0)	109
Malaise/fatigue	9 (8)	3 (3)	0 (0)	111

Note: In addition, there was one report each of Grade 4 dyspnea and mood

Table 4

Pathologic results

	<i>N</i>	%
Total patients	113	100
Pts underwent mastectomy ^a	107	95
Pts with operative report	102	90
Number of positive nodes		
0	24	24
1–3	28	27
4–9	27	26
10+	23	23
Surgical margins		
Negative	8	8
Positive	94	93
Pathologic response		
pCR ^b	5	5
95% CI	2–11	

^aSix patients did not receive mastectomy because of progressive disease, which contraindicated surgery

^bNumbers based on patients with operative reports

Table 5

Pathologic results by clinical response to neoadjuvant doxorubicin

Pathologic results	Clinical response to neoadjuvant dox ^a	
	Response N (%)	Non-response N (%)
# Patients	77 (100)	24 (100)
pN0	20 (26)	4 (17)
pN1–3	21 (27)	7 (29)
pN4–9	22 (29)	5 (21)
pN10+	14 (18)	8 (33)

^aOne patient was not assessable for clinical response; however, she underwent surgery. This patient had 10 or more pathologically involved lymph nodes. She is omitted from this table

Table 6

Grades 2–4 selected toxicities reported during adjuvant CMF

Toxicity type	Grade of toxicity			N with data
	2 (Moderate) N (%)	3 (Severe) N (%)	4 (Life Thr) N (%)	N
Hematologic				
WBC	28 (35)	40 (49)	4 (5)	81
Platelets	9 (11)	5 (6)	1 (1)	81
Hemoglobin	29 (36)	0 (0)	1 (1)	81
Granulocytes	19 (23)	29 (36)	16 (20)	81
Lymphocytes	3 (4)	21 (26)	16 (20)	80
Other				
Cardiac function	1 (1)	3 (4)	0 (0)	78
Infection	11 (14)	2 (3)	0 (0)	80
Nausea	8 (10)	1 (1)	0 (0)	81
Vomiting	8 (10)	1 (1)	0 (0)	80
Diarrhea	9 (11)	0 (0)	0 (0)	80
Stomatitis	8 (10)	5 (6)	0 (0)	81
Transaminase	6 (8)	0 (0)	0 (0)	80
Hematuria	2 (3)	0 (0)	0 (0)	75
Dyspnea	2 (3)	0 (0)	0 (0)	80

Note: In addition, there was one report each of Grade 4 dysrhythmias and partial thromboplastin time