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Pathological Assessment of Response to Induction Chemotherapy in Breast Cancer[1]

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ABSTRACT

Macroscopic and microscopic pathology review was used to assess the degree of tumor reduction after preoperative chemotherapy in 90 patients with inflammatory and locally advanced breast cancer. Fifteen (17%) patients had no evident residual macroscopic tumor on gross pathological examination, and 6 of these 15 had no residual tumor on microscopic review either. There was no significant difference in disease-free and overall survival between the six patients with no microscopic disease and the nine patients with only microscopic residual disease but no residual macroscopic tumor. These 15 patients with major reduction after induction chemotherapy had a longer disease-free survival (DFS) (median not reached at 5 yr) than the other 75 patients with lesser degrees of tumor reduction (DFS = 22 mo; $P < 0.01$).

Clinical evaluation of response to chemotherapy was a less accurate predictor of outcome than was the pathological assessment of response. Complete clinical responders had a 4-yr DFS of 55%, whereas patients with non macroscopic residual tumor following preoperative chemotherapy, less than one-half of whom had been judged to be a complete clinical responder, had a median DFS of >60 mo and a 4-yr DFS of 75%. Patients whose mastectomy specimen had no macroscopic residual disease had a 93% 5-yr survival compared to patients with a less marked response to therapy who had a 5-yr survival of 30% ($P < 0.01$). No pretreatment patient or tumor-related variables correlated with the degree of tumor reduction following preoperative therapy.

Achievement of a mastectomy specimen free of residual macroscopic tumor after preoperative chemotherapy is an excellent prognostic factor for a prolonged DFS and survival. This information should be considered in the selection of postoperative systemic therapy.

INTRODUCTION

Patients with locally advanced breast cancer and inflammatory breast cancer do very poorly when treated solely with locoregional therapy. With either surgery or radiotherapy alone, less than 10% of these patients survive 5 yr (2–6), and the use of combination surgery and radiotherapy yields a median survival of only 2 yr (3, 7) with approximately 20% of patients surviving 5 yr (4, 7). The combined use of mastectomy and radiotherapy generally has led to favorable results for locoregional control with most relapses due to the development of distant metastases (7, 9).

At M. D. Anderson Hospital, patients with inflammatory and locally advanced breast cancer have been treated using a multimodality approach using preoperative induction chemotherapy since 1974. This strategy has lead to a substantial improvement in patient survival, with 35–50% of the patients surviving beyond 5 yr (10–15).

During the past several years, some of our patients receiving preoperative chemotherapy have achieved mastectomy specimens free of residual tumor. These observations prompted an analysis of the impact of achieving a pathological complete response after induction chemotherapy in patients with inflammatory and locally advanced breast cancer.

MATERIALS AND METHODS

Between January 1974 and December 1981, 156 previously untreated patients with locally advanced or inflammatory breast cancer were treated at our institution with a multimodal program. All patients received induction chemotherapy. Prior to 1978, patients only underwent a mastectomy (if there was substantial residual tumor after induction chemotherapy) to facilitate the administration of radiotherapy; however, beginning in 1978, all patients, following induction chemotherapy, were treated initially with mastectomy, with radiation therapy being used for late consolidation. Ninety patients had mastectomy and 66 patients had radiation therapy as the initial local treatment modality following chemotherapy. This study will include the results of the 90 patients who had mastectomy immediately following induction chemotherapy, since the purpose of the study is the pathological evaluation of response to chemotherapy.

All patients underwent an initial staging work-up that included a complete blood count, Chemical Survey (SMA-12), CEA[4] level, chest X-ray, bone survey, bilateral mammography, electrocardiogram, bone, and liver-spleen scans. Blood counts were performed weekly, SMA-12 and CEA before each cycle of chemotherapy, whereas the rest of the work-up was repeated every 3–4 mo during therapy and with decreasing frequency thereafter.

All patients had a biopsy-proven diagnosis of breast cancer and no evidence of distant metastases. They were all clinically staged as T_3 or T_4 and/or N_2 or N_3, M_0, according to the American Joint Commission's tumor-nodes-metastasis classification (2). Patients with a single nonspecific bone scan abnormality were included; all others with abnormal scans were excluded. Patients with the clinical features of inflammatory breast cancer (erythema, peau d'orange, ridging of the skin, and increased local temperature) were included in this study.

All patients received FAC chemotherapy (9). This was administered for three cycles or until maximal (clinically assessed) tumor response was achieved. Peripheral hematological values were assessed at weekly intervals, and the dosage of chemotherapy was adjusted to the degree of myelosuppression. Nonspecific immunotherapy with *Bacillus Calmette-Guérin* was given in the early part of the protocol between 1974 and 1978 but was thereafter deleted. No patient had previous or concomitant hormonal therapy.

An extended simple or modified radical mastectomy was performed 3 wk after the last cycle of induction FAC yielding the maximum clinical response. Postoperatively, the patients resumed chemotherapy with FAC and were maintained on this combination until a cumulative dose of 450 mg/m^2 of doxorubicin had been given. At that time, methotrexate replaced doxorubicin, and this combination was continued until 2 yr of therapy had been completed. Consolidative radiation therapy consisted of 4500–5500 cGy using ^{60}Co or electron beams to the chest wall and to the internal mammary, supraclavicular and axillary lymph nodes (10). Sixty-seven patients received radiation therapy. Of these, 39 patients received radiation therapy immediately after completing surgical therapy, whereas 28 patients received it at the completion of postoperative chemotherapy. A consistent protocol for preparation and assessment of the mastectomy specimen and lymph nodes was performed by the Department of Pathology. A median of 20 sections/mastectomy specimen was assessed; these included sections

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[4] The abbreviations used are: CEA, carcinoembryonic antigen; DFS, disease-free survival; FAC, fluorouracil, Adriamycin (doxorubicin), and cyclophosphamide.

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from each quadrant, from the nipple-areolar complex, from areas of suspicious or prior tumor involvement, and from the axillary contents. Both presence of macroscopic tumor and its size as well as any other histopathological changes in breast parenchyma and the number and size of lymph nodes were assessed.

A complete clinical remission was defined as disappearance of all evidence of tumor, assessed by physical examination, prior to surgery. A partial clinical remission was defined as at least 50% reduction in the sum of the products of the largest perpendicular diameters of measurable lesions without development of new lesions prior to surgery. A gross pathological complete response was defined as the absence of any macroscopic evidence of tumor upon gross inspection of the mastectomy specimen and axillary contents and all sections prepared from them, regardless of the subsequent findings on microscopy. This was assessed independently of the clinical response. Those patients with no macroscopic cancer evident in their mastectomy specimen and axillary contents after inspection of all of their gross pathology sections will be referred to as group A. Those patients with macroscopic evidence of cancer in their mastectomy specimen as determined by the gross pathology examination will be referred to as group B.

DFS was calculated from the date of mastectomy. Survival determinations were calculated from the date chemotherapy was started. The Kaplan and Meier method was used to calculate DFS and survival curves (16), and the generalized Wilcoxon test was used to determine differences between curves (17).

RESULTS

Fifteen of the 90 (17%) patients had no macroscopic evidence of residual gross cancer after thorough review of the mastectomy specimens (group A); additionally, 6 of these 15 patients had no microscopic evidence of cancer in breast or nodal tissue while 2 patients had microscopic residual disease in the breast, 5 in lymph nodes and 2 in both breasts and lymph nodes. Four patients in group A had inflammatory breast cancer. There were no significant differences in the distribution of pretreatment and treatment variables between the 75 patients with (group B) and the 15 patients without (group A) residual macroscopic tumor in their mastectomy specimens (Table 1). Variables assessed included age, menopausal status, initial screening laboratory results (including CEA), tumor and nodal stage, estrogen receptor status, and treatment including radiotherapy, *Bacillus Calmette Guérin* administration and median cycles of FAC prior to mastectomy.

The patients in group A had a significantly longer DFS than the patients in group B (Fig. 1). Group A had a median DFS in excess of 61 mo whereas patients in group B had a median DFS of only 22 mo ($P = 0.002$). With a median follow-up exceeding 5 yr, only 4 (27%) patients without residual macroscopic cancer in their mastectomy specimen (group A) have relapsed. Two of these four patients had microscopic evidence of cancer in their mastectomy specimens.

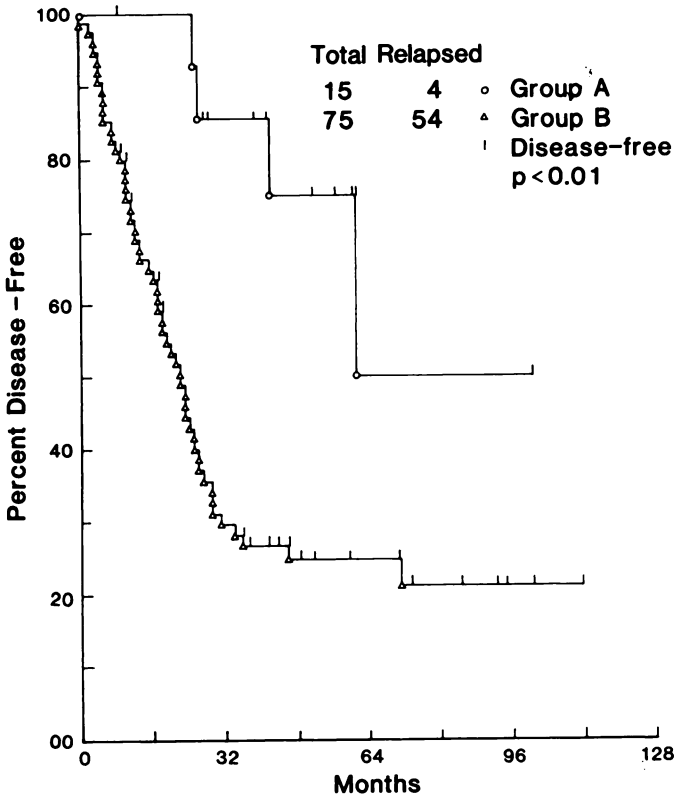

Fig. 1. Disease-free survival according to the presence of gross residual disease on pathological examination following induction chemotherapy; $P < 0.01$.

Twelve % (11 of 90) of the patients had a clinical complete remission and 66% (59 of 90) had clinical partial remission following induction chemotherapy (clinical remissions = 78%).

Six of the 15 patients in group A (those with no macroscopic residual tumor in their mastectomy specimen) had been assessed as having had a clinical complete remission and the other nine patients (in group A) were judged to have had only a clinical partial remission. Five patients from group B had been judged to have a clinical complete remission prior to mastectomy. The 15 patients without residual macroscopic tumor had a higher 4-yr DFS than the 11 with clinical complete remissions (75 *versus* 55%) (Fig. 2). The difference in DFS between groups A and B patients was much greater ($P = 0.002$) than the difference in DFS between clinical complete and noncomplete responders ($P = 0.089$).

The DFS and overall survival of the 90 patients with locally advanced and inflammatory breast cancer included in the report did not differ significantly from the 66 patients who had radiation therapy as the initial local treatment modality following chemotherapy as per our protocol prior to 1978.

Group A patients had a significantly longer survival than those in group B (Fig. 3). Only 3 of 15 patients in group A are deceased. One of these patients had recurrent breast cancer, whereas the other two did not (one had Sheehan's syndrome and died from complications of panhypopituitarism, and the other died from recurrent pulmonary emboli). The projected actuarial survival of the group A patients exceeds 93% at 6 yr if the 2 deceased patients without evidence of recurrence are censored from calculations, whereas it is 34% for patients in group B (median survival of 38 mo; $P = 0.002$) if the 6 patients

Table 1 *Pretreatment patient characteristics*

	Group A[a]	Group B
No. of patients	15	75
Median age and range (yr)	46 (28–68)	54 (28–76)
Median performance status	0	0
Percentage of patients with inflammatory breast cancer	27	25
Percentage of patients with noninflammatory breast cancer	73	75
Percentage premenopausal	53	40
Percentage with abnormal alkaline phosphatase (>85 mμ/ml)	20	33
Percentage with abnormal lactic dehydrogenase (>225 mμ/ml)	13	23

[a] Clinical diagnosis and macroscopic findings in the group with no residual macroscopic disease in mastectomy specimens following induction chemotherapy.

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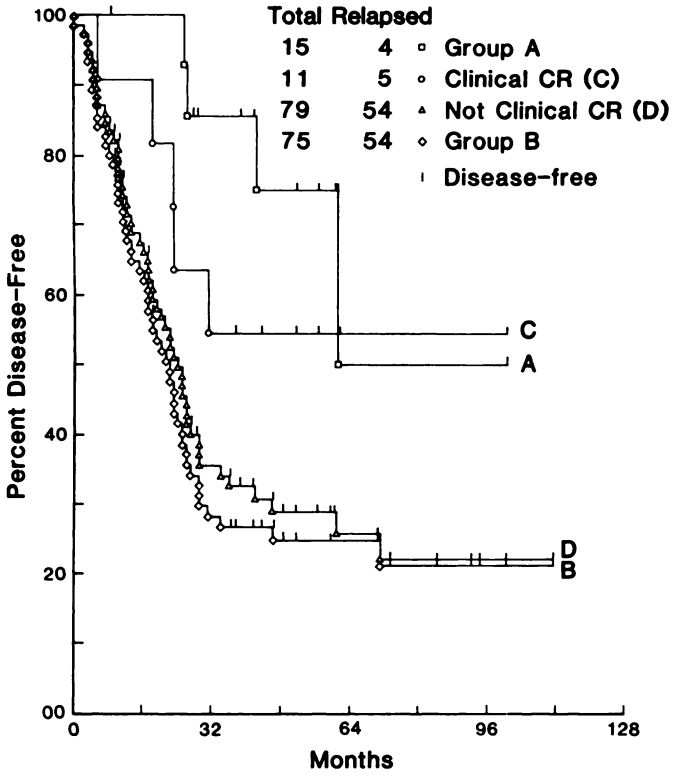

Fig. 2. Disease-free survival of patients in the various response categories: *A*, no residual macroscopic disease on pathology examination; *B*, residual macroscopic disease on pathology examination; *C*, complete clinical response (*CR*); *D*, less than complete clinical response; P (*A versus C*) < 0.05.

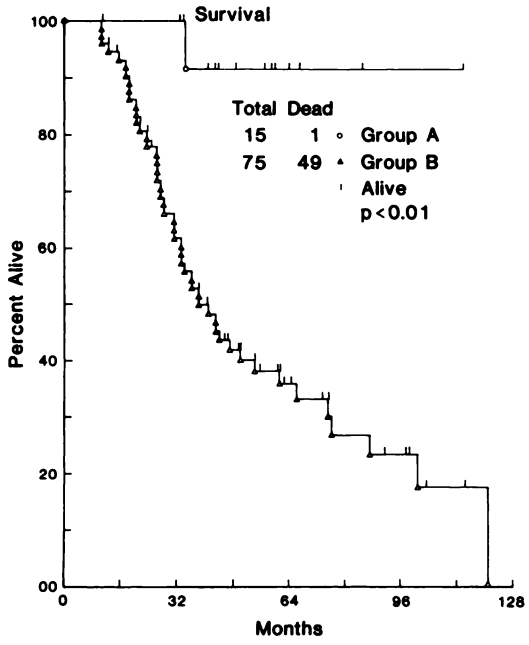

Fig. 3. Survival. Two patients in group A and six patients in group B dead of intercurrent disease are censored (see text); $P < 0.01$.

who died without evidence of recurrent or metastatic disease are censored.

DISCUSSION

A multimodality approach to patients with locally advanced and inflammatory breast cancer has been previously shown to prolong survival over single modality therapy (10–15, 18). The addition of chemotherapy to programs using only surgery and/or radiation therapy has led to the most favorable results for survival of these patients.

There was a 12% clinical complete remission and a 66% clinical partial remission rate to induction chemotherapy. Clinical assessment of response to induction chemotherapy was a relatively poor predictor of outcome. Nine of the 15 patients (in group A) with no macroscopic residual cancer in their mastectomy specimen had been judged by preoperative clincial exam to have residual cancer. This discrepancy may be due to the fibrotic streaks remaining after chemotherapy yielding a clinical impression of residual tumor. Since group A and the group of clinical complete responders share several patients, it is inappropriate to use the Wilcoxon test to compare their DFS or survivals; however, the ability to discriminate between good and poor disease-free survival groups was better for pathological evaluation than for clinical assessment. In this group of 90 patients, the achievement of a mastectomy specimen free of residual macroscopic tumor on gross pathology examination was the most significant factor in predicting for a prolonged disease-free survival ($P = 0.002$) and overall survival ($P = 0.002$).

Benjamin *et al.* (19), Rosen *et al.* (20), and others have recently shown that the degree of pathologically assessed tumor response to preoperative induction chemotherapy in osteogenic sarcoma is one of the most important prognostic factors. Their results and ours suggest the possibility of using the results of preoperative chemotherapy in each patient as an *in vivo* method to assess chemotherapy sensitivity. Pathological assessment of response to induction chemotherapy will suggest whether there is a likelihood of additional benefit to be obtained by continuing the same drugs in the postoperative adjuvant setting. In those patients having an unsatisfactory response to induction chemotherapy (pathologically assessed), different drugs could be tried postoperatively. This approach would hopefully lead to a reduction in unnecessary toxicity from drugs less probable to benefit the patients and possibly to an improvement in the fraction of cured patients.

The complete remission rate in this study was low. New drugs, alternating noncross-resistant combinations, or combined hormonal chemotherapy must be evaluated to increase complete response rate. The preliminary results of a cyclic hormonal chemotherapy program in a similar patient population appear encouraging (21).

Improvement in clinical methods to assess response to induction chemotherapy are sorely needed, especially since a mastectomy may not be necessary for optimal local and sytemic control. In this regard, mammographic or other imaging techniques of response assessment should be explored.

To avoid the usual pitfalls of comparing survival times of responding and nonresponding patients, all patients whose first local therapy was surgery were included in the analysis. This means that all patients have completed at least three cycles of chemotherapy and surgery, eliminating the bias introduced by early deaths and other dropouts; in addition, whereas patients in group A had a markedly improved disease-free and overall survival compared to patients in group B, even patients in group B had disease-free and overall survivals superior to patients treated with local therapies alone (13).

We conclude that accurate assessment of response to induction therapy is the single most important prognostic factor in this group of patients and may provide information necessary to select postoperative adjuvant therapy. This hypothesis is being evaluated in a prospective clinical trial.

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