MAURIE MARKMAN, MD, EDITOR

Chemotherapy in the management of breast cancer

BETH A. OVERMOYER, MD

■ **BACKGROUND** Breast cancer has become a national health problem, affecting more than 180 000 women each year. Although advances in early detection and treatment have been made, it remains the second leading cause of cancer-related death in women.

■ **KEY POINTS** The treatment of breast cancer requires the careful integration of systemic and local methods. Although the application of hormonal therapy or chemotherapy is becoming less distinct, this discussion will review the important clinical trials and future directions of chemotherapy in the management of breast cancer. Data support the use of chemotherapy in the adjuvant setting, for preoperative tumor reduction of locally advanced disease, and as palliation in metastatic disease. The optimal chemotherapeutic regimen is not known; however, data support a role for adjuvant doxorubicin in node-positive disease, neoadjuvant therapy for high-risk disease, and high-dose chemotherapy to consolidate responding metastatic disease.

■ **CONCLUSIONS** The clinician must determine the risks and potential benefits of systemic chemotherapy before recommending treatment strategies. Although progress has been made, future advances can only occur through active participation in clinical trials.

■ INDEX TERMS: BREAST NEOPLASMS; ANTINEOPLASTIC AGENTS
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From the Department of Hematology and Oncology, The Cleveland Clinic Foundation.
Address reprint requests to B.A.O., Department of Hematology and Oncology, T33, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.

THE INCIDENCE of breast cancer has been increasing by 2% to 4% per year over the last decade. This growth appears to be stabilizing and trending toward the baseline increase of 1% per year that has been evident since 1940. The recent surge in incidence rates reflects the early detection pattern obtained by screening mammography; however, other effects cannot be ruled out.[1] In contrast to the relative increase in breast cancer incidence, the age-adjusted mortality rate has remained relatively stable, which may reflect advances in treatment.

Systemic therapy remains the mainstay for breast cancer treatment, although the optimum hormonal and cytotoxic scheme is still unknown. The clinician and patient are currently faced with decisions on breast cancer management that can often become overwhelming. This article will focus specifically on the major advances in chemotherapy and its use in breast cancer, although the reader is cautioned that the future treatment of this disease may not enable a distinction between chemotherapy and hormonal control.

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TABLE 1
AMERICAN JOINT COMMITTEE ON CANCER STAGING SYSTEM FOR BREAST CANCER*

Tumor (T) stage			
T1	Tumor ≤ 2 cm		
T2	Tumor > 2 cm and ≤ 5 cm		
T3	Tumor > 5 cm		
T4	Any tumor size with direct extension to chest wall or skin Includes inflammatory carcinoma		
Nodal (N) stage			
N0	No lymph node metastases		
N1	Metastasis to moveable ipsilateral axillary lymph nodes		
N2	Metastasis to ipsilateral axillary lymph nodes that are fixed to each other or other structures		
N3	Metastasis to internal mammary lymph nodes		
Metastatic (M) stage			
M0	No distant metastases		
M1	Distant metastases Includes metastases in ipsilateral supraclavicular lymph nodes		
Early-stage breast cancer			
Stage I	T1	N0	M0
Stage IIA	T1	N1	M0
	T2	N0–1	M0
Stage IIB	T3	N0	M0
Locally advanced breast cancer			
Stage IIIA	T1–3	N2	M0
	T3	N1	M0
Stage IIIB	T4	Any N	M0
	Any T	N3	M0

*Adapted from Duggan, reference 46

TABLE 2
FIVE-YEAR SURVIVAL BY AGE AND AXILLARY NODE STATUS IN THE NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT*

Number of positive lymph nodes	Survival, %	
	Age ≤ 49 years	Age ≥ 50 years
0	85	82
1–3	73	73
4–6	51	56
7–12	46	52
≥ 13	24	33

*Adapted from Fisher et al, reference 3

EARLY-STAGE BREAST CANCER

Traditionally, early-stage breast cancer was treated by surgical resection alone. However, in the 1970s, two hallmark trials demonstrated a significant relapse rate of distant disease, which was unaffected by radical surgical procedures.[2,3] These data supported the assumption that micrometastatic breast cancer was present at the time of diagnosis. Numerous clinical trials were initiated with the goal of controlling micrometastatic disease in early stage breast cancer using adjuvant ("in addition to surgery") systemic therapy.

The management of stage I or II breast cancer is directed toward a curative goal, both locally and systemically (*Table 1*). Since approximately 70% of patients with early-stage disease do not experience a disease relapse, adjuvant therapy trials have attempted to both identify patients at risk for recurrence and design treatment programs associated with low morbidity. Unfortunately, the overall efficacy of the therapeutic modality may be small when compared with no additional treatment.

Prognostic factors in early-stage breast cancer

The heterogeneity of breast cancer and the variability seen in its clinical behavior require that clinicians formulate some prediction of recurrence risk in early-stage patients. Prognostic factors do not justify but rather guide the clinician in rational adjuvant therapy recommendations outside the context of a clinical trial.

Lymph node involvement. Historically, the most reliable prognostic factor in breast cancer is the number of axillary lymph nodes that are involved with disease. Approximately 40% of newly diagnosed patients will have positive lymph node involvement. The inverse relationship between survival and number of positive lymph nodes is demonstrated in many surgery-alone series (*Table 2*). The quantitative importance of lymph node status cannot be understated.[5] The relative lack of value of "standard" chemotherapy in patients with four or more positive lymph nodes is demonstrated in the 15-year follow-up of the Milan CMF (cyclophosphamide, methotrexate, 5-fluorouracil) trial (*Table 3*).[6]

Whereas the prognostic significance of nodal involvement virtually assures a relapse risk high enough to warrant adjuvant systemic therapy, risk assessment in node-negative patients has become increasingly complex. A substantial number of patients with node-negative disease remain at risk for relapse, as evidenced by 5- and 10-year crude overall survival rates of 87% and 65%, respectively.[7] These patients will benefit from adjuvant therapy; however, rational decision-making regarding systemic treatment in node-negative patients requires that the physician distinguish between established and

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TABLE 3
15-YEAR RESULTS OF CHEMOTHERAPY WITH CYCLOPHOSPHAMIDE, METHOTREXATE, AND 5-FLUOROURACIL*

Number of positive lymph nodes	Control	Chemotherapy	*P* value
Disease-free survival, %			
1–3 nodes positive	31	42	.009
> 3 nodes positive	15	24	.05
Overall survival, %			
1–3 nodes positive	37	48	.08
> 3 nodes positive	24	31	.31

*Adapted from Bonadonna et al, reference 6

TABLE 4
TUMOR SIZE AND RECURRENCE-FREE SURVIVAL IN NODE-NEGATIVE BREAST CANCER WITHOUT CHEMOTHERAPY*

Tumor size, cm	Recurrence-free survival, % 10 years	20 years
≤ 1.0	91	88
1.1–2.0	77	72
2.1–3.0	75	71
3.1–5.0	62	59

*Adapted from Rosen et al, reference 8

investigational prognostic factors.

Tumor size. Ample data exist to demonstrate a subtle but linear increase in systemic recurrence risk with increasing tumor size. This has been demonstrated in both T1 and T2 tumors and confirmed by several studies (*Table 4*).[8]

Estrogen receptor status. Although the evidence for the importance of hormone receptors as prognostic indicators has been conflicting, two large analyses of node-negative patients from the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-06 and the San Antonio data bank show a clear correlation between a positive estrogen receptor and an improved disease-free and overall survival.[9,10] Progesterone receptor status alone does not appear to be an independent prognostic factor in the absence of a positive estrogen receptor; however, this issue remains controversial.

Histologic differentiation. The grading of breast cancer by degree of histologic differentiation has been shown to correlate with relapse risk and survival by several investigators. The classification of breast cancers into categories of nuclear grade ("good"—grade I, vs "poor"—grades II, III) appears to have some prognostic value according to the NSABP.[9] A similar classification and prognostic implication applies to the histologic grade. The importance of nuclear grading is best reserved for grade I tumors, which were associated with a 90% 5-year survival in the NSABP B-06 trial. This grade places patients into a "low risk" category. Although patients with grade II or III tumors may have a higher risk of relapse, interobserver variation in the interpretation of nuclear and histologic grades by the pathologist will always jeopardize the utility of this prognostic factor.

DNA flow cytometry is a laboratory technique that permits rapid evaluation of the quantity of DNA within the tumor relative to a normal cell (ploidy), and the percentage of tumor cells in active DNA synthesis (S-phase fraction). Many studies have attempted to correlate both ploidy and S-phase with clinical outcome in node-negative breast cancer, often with conflicting results. A recent summary by Dressler suggests the inability of ploidy alone to predict a higher risk of relapse. The S-phase calculation consistently predicts a poorer outcome among patients with a "high" value (≥ 6%) vs those with a "low" value. Disease-free survival may be reduced by as much as 20% in such patients.[11]

Investigational factors. A plethora of investigational prognostic factors exist with unknown clinical importance. Some of the most provocative factors associated with a poor prognosis include HER-2/neu oncogene amplification, cathepsin D levels, presence of epidermal growth-factor receptor, tumor angiogenesis factor production, absence of expression of nm23 (the tumor-suppressor gene), detection of bone-marrow micrometastases by monoclonal antibodies, and the expression of p53 gene mutations.

The rational use of the established prognostic factors, and the avoidance of the investigational ones, simplifies the risk-assessment process considerably. McGuire et al have suggested a three-step decision-making process that includes categorizing patients into low-risk and high-risk groups based upon available data, quantifying the benefit from systemic adjuvant therapy, and considering the toxicity of the treatment.[12] The ambiguous nature of assessing overall risk dictates a complete explanation of this process to the patient to ensure that the final treatment is a joint decision.

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Node-negative breast cancer

Between 1981 and 1988, 679 patients with node-negative, hormonally unresponsive (estrogen-receptor-negative) breast cancer were randomized to receive no postoperative systemic therapy or 1 year of chemotherapy with methotrexate, 5-fluorouracil, and leucovorin. This study was performed by the NSABP and designated as trial B-13.[13] The companion trial, B-14, investigated the efficacy of tamoxifen in node-negative, estrogen-receptor-positive patients. The 1993 update of B-13 continued to show that the chemotherapy arm had an advantage in disease-free survival of 10% to 20%, with a marginal survival advantage of 14% confined to the group over 50 years of age.[14]

The most widely used chemotherapeutic regimen in this patient population to date is CMF (cyclophosphamide, methotrexate, and 5-fluorouracil). The NCI Milan's 7-year update of their trial comparing 1 year of CMF adjuvant therapy vs surgery alone continues to confirm the efficacy of this regimen in node-negative patients.[15] Ninety patients were enrolled between 1980 and 1985, and the 7-year follow-up demonstrates a statistically significant decrease in disease relapse (43%) and mortality (28%). The Intergroup trial examined the efficacy of 6 months of adjuvant CMF plus prednisone in this group of patients, and corroborated the NCI Milan's results.[16] The Intergroup trial demonstrated a reduction in disease recurrence with adjuvant chemotherapy; however, the effect on survival awaits further follow-up.

The aforementioned node-negative trials represent a portion of the trials conducted specifically for node-negative disease and provide the framework for the second generation of trials that have only recently completed accrual or are reaching accrual goals. The critical questions being addressed by these trials include: (1) What is the optimum chemotherapy regimen? (2) What is the role of chemohormonal therapy in combination?

Node-positive breast cancer

The number and scope of completed chemotherapy trials for node-positive breast cancer is enormous; however, a discussion of chemotherapy trials would not be complete without mention of the 15-year results of the first NCI Milan CMF program.[6] At this point in the follow-up, a survival advantage continues to be demonstrable and appears to be confined largely to premenopausal patients with three or fewer positive nodes. The relative lack of benefit in postmenopausal women was found to be a reflection of the lower dose intensity that was given to this group (*Table 5*).[17] The poor prognosis associated with the involvement of four or more lymph nodes was reflected in the relative lack of benefit from CMF chemotherapy (*Table 3*).

TABLE 5
DOSE INTENSITY AND RELAPSE-FREE SURVIVAL*

Percent of planned dose of cyclophosphamide, methotrexate, and 5-fluorouracil	5-year relapse-free survival, %
> 85	77
65–84	56
< 65	48

*Adapted from Bonadonna, reference 17

The Overview Analysis

The Overview Analysis of the Early Breast Cancer Trialists' Collaborative Group, published in the *Lancet* in 1992, presents a foundation for general conclusions regarding adjuvant therapy.[4] This meta-analysis combined results from 133 randomized clinical trials involving 75 000 women with early-stage breast cancer. Caution must be used in interpreting the results of the Overview Analysis, since the construct of the trial also included the "test treatment" (ie, tamoxifen) when used with another therapy (chemotherapy) vs the other therapy alone (ie, chemotherapy). For example, the majority of the patients under age 50 who contributed to the tamoxifen Overview also received chemotherapy.

Eleven thousand women were involved in 31 chemotherapy trials. The conclusions derived from the Overview are straightforward: polychemotherapy (consisting of a CMF-based regimen in over 60% of patients) reduces both the rate of recurrence (28%) and mortality (16%) in women of all ages, regardless of nodal status. This mortality reduction is apparent throughout the 10-year period of analysis; it does not appear to diminish but rather enlarges with time. The quantitative value of chemotherapy in reducing mortality is greatest in young patients (under age 50). Shorter courses of chemotherapy were as effective as longer ones (6 months vs 1 year).

By definition, the Overview was not constructed to evaluate combination hormonal therapy and chemotherapy; however, some important conclusions may be drawn by reviewing separately those patients

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who received combination therapy. In patients over age 50, the combination of chemotherapy and hormonal therapy was beneficial relative to chemotherapy alone (over 8000 patients) and over tamoxifen alone (3900 patients), although the margin of benefit over tamoxifen alone was slim (10% reduction in annual odds of death).

Although the Overview provides little data to guide decision-making for individual patients, the generalizations provide a data base against which more compelling clinical questions may be applied. Most of these questions have been addressed or are being addressed in trials for node-positive patients. As the Overview has blurred the distinction between node-positive and node-negative breast cancer, these current outstanding issues will apply to both patient groups.

Anthracycline combinations

The NSABP trial B-15 was conducted from 1984 to 1988 to compare 6 months of adjuvant CMF chemotherapy with 3 months of a doxorubicin-containing regimen, AC (doxorubicin and cyclophosphamide).[18] The premise of this trial was based upon the finding that doxorubicin chemotherapy was the most effective drug for metastatic breast cancer and, therefore, should be more effective in reducing the rate of relapse and mortality among node-positive patients. This concept was supported by two NSABP trials, B-11 and B-16.[19,20] The 3-year follow-up of the NSABP trial B-15 showed no difference in any group with respect to disease-free or overall survival. The similarity in toxicity among all regimens has raised a distinct possibility of the AC regimen replacing the CMF regimen.

The Oncofrance Trial is the oldest trial randomizing patients to receive a conventional chemotherapy vs a doxorubicin-based regimen.[21] Between 1978 and 1981, 249 patients were randomized to receive either 1 year of CMF or 1 year of AVCF (cyclophosphamide, doxorubicin, 5-fluorouracil, and vincristine). Ten-year results suggest an improved survival for patients receiving doxorubicin, though the benefit was largely confined to premenopausal patients. The addition of doxorubicin reduced the risk of relapse by one third and reduced the risk of death at 10 years by one half.

Two additional large trials supported the efficacy of doxorubicin chemotherapy in node-positive breast cancer. One trial compared a doxorubicin-containing regimen with a conventional CMF-based regimen in 532 premenopausal patients.[22] Each treatment was given for 1 year, and all patients received concurrent tamoxifen therapy for differing lengths of time according to a second randomization. With the median follow-up time of 6 years, a reduction in disease relapse was seen with the use of the doxorubicin-containing regimen.

The marginal value of the standard CMF regimen among patients with more than three positive lymph nodes demonstrated in the first NCI Milan program led to a trial in which doxorubicin was used as a single agent followed by CMF ("sequential" regimen), and was compared with alternating CMF and doxorubicin ("alternating" regimen).[23] A 5-year survival advantage was seen among the group receiving "sequential" drug administration (78% vs 62%). This effect was more pronounced in the postmenopausal and estrogen- and progesterone-receptor-negative patients.

These and other studies currently support the use of doxorubicin adjuvant therapy regimens as "suitable alternatives" rather than "superior alternatives" to CMF-based chemotherapy. The Intergroup Trial 0102 will answer this question in the node-negative population. For now, many practitioners will continue to apply doxorubicin-based therapies in node-positive patients, particularly in patients with more than three positive lymph nodes.

DOSE INTENSITY

Dose intensity can be defined as the total dose of chemotherapy received (mg/m^2) per unit of time. Preclinical studies have consistently demonstrated a correlation between increased cancer cell-kill and dose intensity.[24] Several retrospective analyses have applied the concept of dose intensity to clinical results of breast cancer relapse and survival.[25] Bonadonna's retrospective analysis of the first NCI Milan CMF trial suggested a compromise in survival among patients who did not receive "full or nearly full" doses of CMF (*Table 5*).[17] In addition, Hyriniuk evaluated 3-year disease-free survival resulting from several different CMF-containing regimens used for adjuvant chemotherapy.[26] A linear increase in duration without disease relapse was seen among patients receiving more dose-intense regimens. This relationship between dose intensity and disease response is highly provocative and forms the basis of several trials comparing the efficacy of conventional chemotherapy with high-dose chemotherapy and

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autologous bone marrow rescue among patients with an increased risk of relapse.

The first study in which dose intensity was evaluated in the adjuvant setting was published in 1992.[27] This study includes over 1500 patients of all ages with positive lymph nodes. Patients were randomized to one of three CAF (cyclophosphamide, doxorubicin, 5-fluorouracil) regimens with separate dose intensity. The 3-year results show a statistically significant improvement in disease-free survival (75% vs 64%), and overall survival (92% vs 84%) when the higher dose treatment is compared with the lower dose. No such significance has been shown between high and moderate dose levels. However, the dose intensity of the "low-dose" arm would be considered inadequate by today's standards.

The French Adjuvant Study Group initiated a dose intensity adjuvant therapy trial in 1986, randomizing nearly 600 premenopausal patients onto one of three treatment regimens that differed in doses.[28] No difference in recurrence rate or survival has been observed at a median follow-up of 37 months. These results have also been supported by two trials at the M.D. Anderson Cancer Center that analyzed the efficacy of dose intensity among doxorubicin-containing regimens.[29,30] The failure of these trials to demonstrate a consistent benefit of dose intensity may reflect the narrow range of dose increase. Currently, the use of dose-intense conventional chemotherapy in the adjuvant setting should only be utilized in the context of a clinical trial.

AUTOLOGOUS BONE MARROW TRANSPLANTATION

The application of high-dose chemotherapy followed by autologous bone marrow rescue is being applied for treatment of patients with high-risk breast cancer, such as those having 10 or more positive axillary lymph nodes. Standard-dose chemotherapy has not significantly improved the grim outcome associated with breast cancer involving many axillary lymph nodes, as previously discussed. With the aim of improving the benefits of adjuvant chemotherapy, Peters from Duke University treated 85 patients with stage II or III breast cancer involving more than 10 lymph nodes with adjuvant AC chemotherapy followed by intensification ("high-dose" chemotherapy) using cyclophosphamide, cisplatin, and carmustine with autologous bone marrow rescue.[31] At 2.5 years of follow-up, 72% of patients experienced event-free survival.

These results were historically compared to three adjuvant conventional-dose chemotherapy trials involving over 240 similar patients. The conventional-dose trials had an associated relapse-free survival between 38% and 52%, compared with the result of 72% among those patients who received high-dose chemotherapy with autologous bone marrow support. The relatively short follow-up does not permit sweeping conclusions regarding the value of high-dose chemotherapy in patients at high risk for relapse; however, the data are provocative.

Two ongoing randomized cooperative studies are examining the efficacy and toxicity of high-dose chemotherapy and autologous bone marrow support in women with 10 or more positive lymph nodes. One trial uses standard CAF adjuvant chemotherapy followed by a randomization to high-dose chemotherapy and autologous bone marrow support vs observation alone. A second trial also uses standard CAF adjuvant chemotherapy followed by a randomization to high-dose chemotherapy plus autologous bone marrow support vs a "lower dose" regimen of cyclophosphamide, cisplatin, and carmustine not requiring autologous bone marrow support.[32] Again, the use of this modality in the adjuvant setting requires investigation through participation in clinical trials.

LOCALLY ADVANCED BREAST CANCER

Although breast cancer screening has been vigorously and widely advocated, 10% to 20% of women diagnosed with breast cancer continue to present with locally advanced disease. This is a heterogenous category of breast cancer, encompassing large tumor sizes, extensive axillary lymph-node involvement (ie, stage IIIA and stage IIIB), or inflammatory breast cancer (*Table 1*). The latter entity is clinically distinct from locally advanced breast cancer and will be addressed further on.

As with stage I and stage II breast cancer, the treatment goal for locally advanced breast cancer is curative. This goal dictates the use of both local and systemic disease control. Historically, the combination of radiation and surgery improved the local recurrence rate of breast cancer (chest wall and regional lymph nodes); however, local therapy alone was associated with a dismal survival rate (*Table 6*).[33] There are few randomized trials that have investigated the benefit of adding systemic therapy to local treatment. In addition to the pau-

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TABLE 6
5- AND 10-YEAR SURVIVAL IN LOCALLY ADVANCED BREAST CANCER*

Treatment	5-year survival, %	10-year survival, %
Surgery	41	19
Radiation	29	23
Surgery and radiation	33	22

*Adapted from Hortabagyi, reference 33

city of data, most of these trials are flawed because of their use of ineffective chemotherapy regimens.[34,35] Some mention of these pioneering investigations is warranted.

Between 1979 and 1985, the European Organization for Research and Treatment of Cancer investigated the contribution of chemotherapy and hormonal therapy to primary radiation therapy in 363 women with locally advanced breast cancer.[36] Patients were randomized to radiation therapy alone, radiation followed by chemotherapy (CMF for 12 months), radiation followed by hormonal therapy (either tamoxifen or ovarian ablation), or radiation followed by concurrent chemohormonal therapy. The combination of hormonal therapy and chemotherapy significantly increased the time to local and regional disease recurrence, although the hormonal contribution was only seen among estrogen-receptor-positive patients. The major effect of systemic therapy in this trial was to delay the local disease recurrence; a decrease in distant recurrence and mortality was seen, but this was not statistically significant.

Neoadjuvant chemotherapy for locally advanced cancer

The results from these early trials were provocative and stimulated speculation concerning the optimum timing of multimodality treatment. The use of "induction" or "neoadjuvant" chemotherapy has become an accepted treatment approach among clinicians, although because of the diverse nature of locally advanced breast cancer, chemotherapy use as the initial cytoreductive treatment remains controversial.[37,38] The purpose of neoadjuvant chemotherapy is two-fold: (1) to reduce local tumor bulk, thereby avoiding surgical dissection through skin and soft tissue involved with cancer; and (2) to effectively eliminate micrometastatic disease before drug-resistant clones develop. Theoretically, optimal tumor reduction occurs by avoiding the time delay

TABLE 7
DOXORUBICIN CHEMOTHERAPY FOR LOCALLY ADVANCED BREAST CANCER*

Regimen	Tumor response, %	Overall survival, % (years)
Cyclophosphamide, doxorubicin, 5-fluorouracil, vincristine, prednisone	69	35 (5)
5-Fluorouracil, doxorubicin, cyclophosphamide	67–87	50 (2)
Doxorubicin, vincristine	54	50 (4)
Vinblastine, thiotepa, methotrexate, 5-fluorouracil, doxorubicin, prednisone	91	75 (4)

*Adapted from Piccart et al, reference 44

associated with local disease treatment and by eliminating the potential for ineffective tumor perfusion due to vasculature changes brought about by surgery or radiation therapy.[39,40] In addition, neoadjuvant chemotherapy gives the clinician a unique opportunity to use clinical tumor response as an in vivo guide to the effectiveness of systemic treatment.

The M.D. Anderson Cancer Center treated 174 women with locally advanced breast cancer using a combined modality approach initiated by FAC (5-fluorouracil, doxorubicin, cyclophosphamide) chemotherapy.[41] The clinical response to neoadjuvant chemotherapy was assessed after three cycles of FAC, and local therapy was performed with radiation therapy, surgery (modified radical mastectomy), or both. Once adequate local recovery was achieved, FAC chemotherapy continued to a maximum doxorubicin dose of 450 to 500 mg/m^2, then was replaced with CMF chemotherapy. Systemic therapy initially encompassed 2 years; however, the duration was later reduced to a total of 9 months. No difference in response was seen with respect to the duration of chemotherapy. At 5 years, 71% of stage IIIA and 33% of stage IIIB patients were free of disease. The 5-year overall survival for stage IIIA and IIIB patients equalled 84% and 44%, respectively.

Several other studies have confirmed the benefit of neoadjuvant chemotherapy for locally advanced breast cancer.[39,42,43] Based on these data, most clinicians utilize a multimodality treatment approach, beginning with four to six cycles of a doxorubicin-containing chemotherapy regimen, which contin-

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ues until maximal tumor reduction is demonstrated by physical exam and mammography. The greatest tumor response appears to be associated with doxorubicin-containing chemotherapy (*Table 7*).[44] Local therapy follows, although the exact sequencing of surgery and radiation therapy has not been defined. Radiation therapy is given to the involved breast and regional lymph nodes. Surgical treatment is either with modified radical mastectomy or breast-conserving surgery (tumorectomy and ipsilateral axillary lymph-node dissection). Chemotherapy is continued after recovery from local treatment, although the total duration of systemic therapy is controversial. Most investigators have documented a benefit in continuing treatment with either the preoperative chemotherapy regimen or CMF, for a total duration of 9 to 12 months.

TABLE 8
PROGNOSTIC FEATURES IN LOCALLY ADVANCED BREAST CANCER*

Number of positive lymph nodes	Actuarial 5-year survival, %
0	70
1–3	62
4–10	47
> 10	21
Clinical response	**Actuarial 5-year survival, %**
Complete	94
Partial	47
Pathologic response	**Actuarial 5-year survival, %**
Negative, microscopic	65
Gross	49

*Adapted from McCready et al, reference 52

Local disease control

Data repeatedly confirm the lack of influence that local breast cancer treatment has on survival outcome. From 1978 to 1983, 113 patients received three cycles of neoadjuvant CAFVP (cyclophosphamide, doxorubicin, 5-fluorouracil, vincristine, prednisone). If the tumor was operable as a result of regression from the neoadjuvant chemotherapy, patients were randomized to surgery or radiation therapy.[45] Chemotherapy continued for 2 years once the local treatment was concluded. The duration of disease control or survival was not influenced by the modality of local treatment, ie, radiation or surgery.

The advantage of neoadjuvant chemotherapy has now expanded to include its utility in transforming inoperable stage III breast cancer into operable disease amenable to breast conservation.[47–50] However, the role of breast conservation in locally advanced breast cancer is extremely controversial, and should only be utilized in the setting of a clinical trial.

Prognostic features in locally advanced cancer

The M.D. Anderson Cancer Center found prognostic value in pathologic features found at mastectomy following neoadjuvant FAC chemotherapy.[52] One hundred thirty-six patients were given three to six cycles of FAC chemotherapy, then underwent modified radical mastectomy. The number of ipsilateral axillary lymph nodes involved with disease after preoperative chemotherapy remains the most significant prognostic factor for both disease recurrence and overall survival. Twenty-five percent of patients treated with neoadjuvant FAC were rendered node-negative at the time of surgery. This group was found to have the most favorable prognosis, suggesting that the pathologic assessment of lymph nodes can be utilized to predict the efficacy of other preoperative chemotherapy regimens currently being investigated and to identify high-risk patients who would benefit from continued systemic therapy following local treatment.

Other favorable prognostic features include no residual disease or microscopic disease within the mastectomy specimen. Neither clinical nodal involvement at the time of diagnosis nor estrogen receptor status was predictive of disease response (*Table 8*).

Inflammatory breast cancer

Although inflammatory breast cancer is classified as locally advanced disease, its clinical course differs significantly enough from stage III disease to justify an independent discussion of treatment. Inflammatory breast cancer accounts for only 1% to 4% of all breast cancer, and its prognosis is extremely poor when treated with local therapy alone. The 5-year survival rate is only 10% with surgery alone, and although the local control is improved with the addition of radiation therapy, most studies continue to show a grim 0% to 20% 5-year survival.[40] As with other locally advanced breast cancers, the use of hormonal therapy in inflammatory breast cancer does not significantly reduce mortality, and chemotherapy becomes the mainstay of treatment.

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TABLE 9
RESULTS OF COMBINED THERAPY FOR INFLAMMATORY BREAST CANCER

Investigator	Disease-free survival at 5 years, %	Overall survival at 5 years, %
Fields[54]	37	48
Fowble[55]	—	47
Antman[56]	43	—

From 1973 until 1982, 230 women with inflammatory breast cancer at the Institut Gustave-Roussy were randomized to receive radiation therapy, chemotherapy alone with AVM (doxorubicin, vincristine, methotrexate), or a dose-intensive combination of AVCMF (doxorubicin, vincristine, cyclophosphamide, methotrexate, 5-fluorouracil) and radiation.[53] Patients receiving chemotherapy were treated with three cycles before local therapy and five cycles after local therapy. The 4-year survival was 28% among those receiving local therapy alone. A statistically significant improvement in mortality was demonstrated among those individuals receiving chemotherapy. The 4-year survival was 44% for patients treated with AVM chemotherapy and 66% for those receiving AVCMF. This study not only supports a benefit for induction and maintenance chemotherapy for inflammatory breast cancer treatment, but suggests that dose intensity may also reduce mortality.

Based on several studies using induction chemotherapy followed by radiation therapy, surgery, and maintenance chemotherapy, the 5-year disease-free and overall survival have significantly improved, ranging from 22% to 48% and 30% to 75%, respectively (*Table* 9).[40,54,55]

Autologous bone marrow transplantation

Ongoing clinical trials are attempting to determine the efficacy of consolidating disease response from induction (neoadjuvant) chemotherapy with high-dose chemotherapy and autologous bone marrow transplantation. Individuals with stage III disease are also eligible for a trial described above in the section on dose intensity. The total numbers of patients available for clinical trials directed toward locally advanced or inflammatory breast cancer are too small to enable the completion of large randomized trials within acceptable time limits. Studies using high-dose chemotherapy have only recently accrued sufficient numbers of patients to present preliminary results, and the follow-up remains too short to determine the effect on mortality.

Antman and her colleagues reported on the early results of consolidation high-dose chemotherapy with autologous bone marrow rescue following induction chemotherapy among 56 women with locally advanced or inflammatory breast cancer.[56] At the time of data analysis, 43% had achieved a continuous complete response. The prolonged disease-free interval will hopefully translate into a prolonged overall survival; however, the follow-up is too short to comment upon the survival response. Two preliminary reports using high-dose chemotherapy with autologous bone marrow rescue as consolidation for inflammatory breast cancer support Antman's results.[57,58] A longer follow-up is necessary before this therapeutic modality becomes routinely accepted.

Although the application of combination therapy for locally advanced breast cancer has significantly reduced mortality, the survival statistics remain poor. Further investigation is needed to determine the optimal neoadjuvant chemotherapy regimen, the optimal duration of both preoperative and postoperative chemotherapy, and the role of high-dose consolidation chemotherapy (with or without autologous bone marrow support). Questions remain concerning the optimal timing of radiation therapy, the role of breast conservation, and the optimal role of hormonal therapy in locally advanced and inflammatory breast cancer.

METASTATIC DISEASE

Unlike in other stages of breast cancer, the treatment goal for metastatic disease is palliative, since patients with recurrent disease are essentially incurable. Although a large number of clinical trials address innovative treatment with biologic modifiers, dose-intensive chemotherapy, and hormonal therapy, survival outcomes have been static, and the median survival continues to be approximately 2 years. To complicate matters, many patients have developed recurrent disease after adjuvant chemotherapy, making drug resistance a potential problem.

The judicious use of chemotherapy for disseminated disease can prolong symptom-free intervals and improve quality of life. An understanding of drug toxicity and objective documentation of disease response is vital in order to avoid therapeutic side effects from ineffective treatment. The integration of local treatment (ie, surgery and radiation therapy),

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hormonal manipulation, and chemotherapy utilizes the clinician's skill in the art of medicine.

Combination chemotherapy

The disease-free interval, ie, the duration between the completion of adjuvant therapy and relapse, is an important feature, since patients who relapse later than 12 months after adjuvant therapy have a 50% response rate to the same chemotherapy given initially as adjuvant treatment. Doxorubicin can salvage approximately 40% of patients who relapse within 12 months of adjuvant treatment.[59] Doxorubicin (or the European equivalent, epirubicin) continues to be the most active agent for recurrent breast cancer, although studies are ongoing which will compare its efficacy to a new agent, paclitaxel. Doxorubicin-containing regimens are associated with 10% to 20% higher response rates compared with other effective first-line chemotherapy combinations containing methotrexate. Unfortunately, long-term doxorubicin therapy is restricted by a maximal lifetime dose (450 to 500 mg/m^2), above which there is a risk of congestive heart failure.

Another anthracycline, mitoxantrone, was developed with the hope of retaining efficacy without the associated cardiotoxicity. Three hundred and twenty-five women with metastatic breast cancer at the Dana Farber Cancer Institute were randomized between single-agent mitoxantrone and single-agent doxorubicin. Significantly less cardiotoxicity was confirmed, but the efficacy was slightly less for mitoxantrone.[60] When combination chemotherapy using CAF was compared with CNF (cyclophosphamide, mitoxantrone, 5-fluorouracil), similar results were seen: the mitoxantrone-containing regimen was slightly less effective than the doxorubicin-containing regimen (not statistically significant); however, the former regimen caused less adverse effects.[61] These data prompted the exchange of mitoxantrone for doxorubicin in several investigative second-line salvage regimens.[62,63]

Other combinations of chemotherapy have also been effective in palliating metastatic breast cancer. However, once a patient progresses after receiving doxorubicin, the probability of a durable response to a third-line regimen is small. The combination of vinblastine and mitomycin C has a 23% response rate among heavily pretreated patients; however, the bone marrow suppression associated with prolonged mitomycin C treatment makes this combination difficult to administer.[64] Early trials with cisplatin and etoposide suggested a 25% response rate when used as third-line therapy, with a slightly higher response rate when used earlier in the treatment course.[65,66] Carboplatin has slight efficacy in the first-line treatment of metastatic disease and scant benefit for previously treated patients.[67,68]

Paclitaxel

Paclitaxel is the newest agent for breast cancer treatment that has been associated with response rates similar to that of doxorubicin. Paclitaxel is a microtubule toxin that is derived from the Pacific yew tree. The efficacy of this drug was initially limited by hypersensitivity reactions; however, these occurrences are now avoided by antiallergic medications. The M.D. Anderson Cancer Center treated 25 patients with metastatic breast cancer who had received one prior chemotherapy regimen, either adjuvantly or for relapsed disease.[69] All but two patients had been exposed to doxorubicin. The overall response rate was 56%, with 12% achieving a complete remission.

These significant response rates were confirmed by the Memorial Sloan-Kettering Cancer Center.[70] Paclitaxel was administered as first-line therapy to 28 patients with metastatic disease and resulted in a 62% overall response rate. As in the M.D. Anderson series, 12% of the patients achieved a complete remission. Because of the limited availability of paclitaxel during this trial, patients were unable to receive prolonged treatment; therefore, response duration and survival could not be assessed.

Autologous bone marrow transplantation

In an attempt to improve upon the poor response rates of conventional chemotherapy in the treatment of metastatic breast cancer, high-dose chemotherapy was investigated because of its utility in overcoming drug resistance. Preliminary results are intriguing; however, they lack direct comparison with standard regimens. The Philadelphia Bone Marrow Transplantation Trial is currently randomizing patients who have hormone-refractory metastatic disease that is responsive to induction chemotherapy to either consolidation high-dose chemotherapy with autologous bone marrow rescue or 2 years of conventional-dose CMF. This trial will not only answer pertinent questions concerning the efficacy and toxicity of high-dose therapy, but will also determine the effect of treatment on quality of life and economics.

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Few data address the optimal duration of chemotherapy for relapsed breast cancer. Wake Forest University investigated this issue among 250 women with metastatic disease.[71] All patients were initially treated with FAC chemotherapy, then randomized to either "maintenance" CMF until disease progression or no further therapy. Continuous chemotherapy was associated with a prolonged time to disease progression when compared with induction chemotherapy and observation (9.4 months vs 3.2 months). The mortality was equal in both groups. Coates confirmed a delay in disease progression with continuous chemotherapy and also found that quality of life was improved among patients receiving ongoing treatment.[72]

Advocates of high-dose chemotherapy with or without autologous bone marrow rescue claim that quality of life will improve among women receiving a brief but intensive course of treatment. In addition, preliminary data suggest a prolonged disease-free interval resulting from high-dose chemotherapy, which may translate into an increased overall survival. The University of Chicago enrolled 59 patients with previously untreated relapsed breast cancer from 1986 to 1989.[73] Induction chemotherapy was given to determine chemosensitivity. Patients with responsive disease underwent high-dose chemotherapy consolidation using either cyclophosphamide and thiotepa or cyclophosphamide, thiotepa, and carmustine. At a follow-up of over 4 years, the median survival was 15 months.

Investigators at the Dana Farber Cancer Institute also determined the efficacy of high-dose chemotherapy consolidation among women with metastatic disease responding to conventional-dose chemotherapy.[74] Twenty-nine patients with chemosensitive disease received high-dose cyclophosphamide, carboplatin, and thiotepa. The time to disease progression was 15 months among women achieving a complete remission, but only 5 months for those with a partial disease remission. The effect on overall survival cannot be determined because 15 of the 29 patients are alive at more than 2 years of follow-up.

A recent review of published data on high-dose chemotherapy with autologous bone marrow rescue for women with relapsed breast cancer supports conclusions that differ from individual trial results.[75] Due to the lack of direct comparison between high-dose chemotherapy and standard-dose chemotherapy, the authors performed gross comparisons of the treatment outcomes independently reported. Understandably, this type of comparison is fraught with statistical uncertainty, but its provocative analysis warrants comment. The authors concluded that high-dose chemotherapy with autologous bone marrow rescue achieves higher complete response rates when compared with conventional-dose chemotherapy, 36% vs 8%. The high-dose regimen is also associated with an increased overall response rate, 70% vs 39%. Interestingly, high-dose chemotherapy with autologous bone marrow rescue and conventional-dose chemotherapy treatment resulted in similar outcomes with respect to median response duration, median survival duration, and overall survival rate. Again, the underlying analysis has many flaws; however, it is presented to stress the strictly investigational nature of high-dose chemotherapy for consolidation in metastatic breast cancer.

Sequential high-dose chemotherapy with autologous bone marrow rescue

An interesting principle of tumor-cell kinetics is currently being applied to the treatment of metastatic breast cancer. Although preliminary studies with high-dose chemotherapy and autologous bone marrow rescue suggest a prolonged disease-free interval, overall survival may not be improved because of the theoretical inability of a single cycle of chemotherapy to eradicate all tumor cells, thus permitting the rapid regrowth of the few remaining cancer cells based on Gompertzian kinetics. For this reason, several cycles of high-dose chemotherapy may be able to eradicate all clones of cancer cells as they regrow.

This treatment approach has been investigated by the Memorial Sloan-Kettering Cancer Center.[76] Seventeen patients with heavily pretreated metastatic breast cancer received three cycles of high-dose cyclophosphamide followed by autologous bone marrow support with peripheral stem cells. Seven patients had assessable disease. Among these seven patients, two achieved a complete remission, and four obtained a partial remission. These results are interesting because of the response seen in highly treated patients. This treatment remains investigational.

TOXICITY

Each chemotherapeutic agent used in breast cancer treatment has its own unique toxicity. A complete discussion of the potential complications of

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each drug is beyond the scope of this manuscript. Therefore, only the most common or most serious consequences of systemic chemotherapy will be addressed.

Second malignancies

The association between melphalan adjuvant chemotherapy and an increased risk of acute leukemia is well known.[77,78] The long-term toxicity of more conventional regimens has been reviewed by the National Cancer Institute of Italy.[79] Iatrogenic morbidity was examined among more than 2000 patients treated with adjuvant CAF or CMF chemotherapy between 1973 and 1990, with a median follow-up of approximately 5 years. No patients received tamoxifen.

The incidence of acute leukemia and second malignancies (excluding contralateral breast cancer and basal cell skin cancer) has been evaluated after a 15-year follow-up. The incidence of acute leukemia was 0.25% (3 of 2465 patients). Most of the secondary solid tumors were gastrointestinal and genitourinary malignancies. These occurrences were so rare that the conclusion was that adjuvant chemotherapy does not increase the incidence of second neoplasms.

Cardiovascular effects

The cardiac effects of adjuvant chemotherapy were evaluated as well. Cardiac toxicity is generally more pronounced in patients receiving left breast radiation, particularly among those receiving doxorubicin. The actual risk of myocardial toxicity was 0.5%. Transient and reversible ST-T changes were the most common abnormalities seen, occurring in 70% receiving chemotherapy.[79]

As previously mentioned, the cardiotoxicity associated with doxorubicin chemotherapy is proportional to the cumulative dose. Adjuvant chemotherapy usually achieves a total dose of 240 to 400 mg/m^2. The risk of congestive heart failure is 0.1% to 1.2% up to the maximal dose of 550 mg/m^2, and 30% with higher doses.[78] Still, the overall risk of heart failure is rare (0.4% to 0.9%), but may increase with the use of high-dose chemotherapy.

Amenorrhea

The incidence of amenorrhea in 508 premenopausal patients is reported as 76%. The actual incidence is age-related, occurring in only 50% of patients age 36 to 40, 86% of patients between age 41 and 45, and 100% of patients over age 45. Only 4% of patients under age 36 develop amenorrhea.[78] The contribution of amenorrhea to the efficacy of adjuvant chemotherapy is a subject of ongoing controversy. The apparent value of chemotherapy in postmenopausal patients and its quantitatively greater value in premenopausal patients casts doubt on the exclusive role of amenorrhea as the therapeutic effect of chemotherapy.

Systemic effects

All chemotherapeutic agents are associated with varying degrees of neutropenia, alopecia, and risk of infection. Supportive measures, such as the use of colony-stimulating factors, will hopefully reduce the toxicity associated with bone marrow suppression caused by chemotherapy. Newer antiemetics effectively control nausea and vomiting.

Mortality

Conventional-dose chemotherapy, such as that used in the adjuvant setting, is associated with an extremely low risk of death (< 1%). In contrast, high-dose chemotherapy with autologous bone marrow rescue has treatment-related mortality rates of 0% to 25% (mean of 12%). These data are improving with the progressive supportive measures now available.[75]

CONCLUSION

Breast cancer has become a national health problem, affecting more than 180 000 women each year. Systemic therapy can significantly alter the course of the disease; however, the optimal treatment has not been determined. The integration of chemotherapy with hormonal therapy is an ongoing research question. In addition, the role of dose intensity still requires long-term follow-up to determine the risk-benefit ratio.

This manuscript has only addressed the role of systemic chemotherapy in the treatment of breast cancer. The reader is reminded that the optimal treatment of this disease requires the integration of several therapeutic modalities: surgery, radiation therapy, hormonal therapy, and chemotherapy. With a further understanding of this disease, the subtle differences in the application of multimodality treatment may become blurred.

The current use of chemotherapy, both in the adjuvant and metastatic setting, requires a full re-

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alization of the expected benefit in prolonging time without disease and overall survival, as well as a thorough understanding of related short-term and long-term toxicity and its effect upon quality of life.

This complex interaction of factors makes the doctor-patient relationship vital in determining acceptable treatment options.

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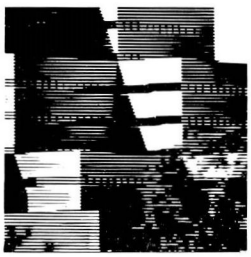

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