Breast Cancer: An Update

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Breast cancer comprises approximately 13.9% of all cases of malignancy in both sexes and 19% in women, in whom it is the commonest form of cancer.[1] The American Cancer Society estimates that 110,000 women developed breast cancer in 1981, and some 37,100 deaths from the disease occurred.[2] The five-year survival rate has been improving over the past 40 years as shown in Table 1[1], but patients remain in risk of recurrence indefinitely, and survival for ten years is generally accepted as the minimal time period necessary to establish the validity of new therapies.

Data from the first study of the National Surgical Adjuvant Breast and Bowel Project (NSABP) are shown in Table 2 and indicate that the majority of women with breast cancer ultimately succumb to the disease.[3] Thus, although only 10% of cases present with metastatic disease (an additional 5% predictably have very rapid progression: inflammatory carcinoma, extensive local or regional disease), over half of those undergoing mastectomy will develop recurrence within ten years.

The identification of women with either adverse or favorable prognostic features modifies these figures considerably. Among the important favorable variables are: attainment of menopausal status for at least five years; increasing age; primary tumors two cm in diameter or less; absence of regional node involvement; estrogen and progesterone receptor positivity and, for estrogen receptors at least, absolute amount of receptor; delay between initial presentation and recurrence; skin or nodal local recurrence as opposed to visceral metastasis; and perhaps most important, an overall less aggressive biological character of the tumor.

Adverse prognostic features include: a clinical picture of inflammatory carcinoma; concurrent pregnancy; liver metastasis; multiple visceral metastases at presentation; brain, meningeal, epidural involvement, or spinal cord compression secondary to vertebral collapse; lymphangitic pulmonary spread; absence of estrogen and, possibly, progesterone receptor; failure of previous therapy for systemic disease; and inability to withstand the toxicities associated with chemotherapy or hormonal therapy. An excellent review of all phases of breast cancer has recently been published.[5]

I intend to concentrate on four areas in greater detail: 1) the usefulness of receptor assays in predicting the response to therapy; 2) chemotherapy of advanced metastatic disease; 3) adjuvant chemotherapy following surgery; 4) the usefulness of antiestrogens in hormonally-responsive disease.

Receptor Assays

Steroid hormones are known to act by crossing the cell membrane where they bind to specific cytoplasmic receptors. The receptor-steroid complex is activated and translocates to the nucleus where it interacts with chromatin.

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TABLE 1
Five-Year Survival Rates in Breast Cancer

1940–1949	53%
1953–1959	60%
1960–1964	62%
1965–1969	64%

(*Note:* Adapted from Cutler SJ, Myers, MH, Green SB: Trends in survival rates of patients with cancer. *N Engl J Med* 293: 122–124, 1975.) **(By Permission)**

As a result of this interaction, RNA synthesis is increased and new proteins are synthesized.[6] It now seems that the appearance of progesterone receptors in breast tumors is the result of estrogen stimulation and is a measure of hormonal responsiveness (Table 3).[7]

The presence of estrogen receptor (ER) is an important determinant of prognosis independent of the effects of age, nodal involvement and primary lesion size (Table 4). The ER level is less in the tumors of younger women and is less in primary as opposed to metastatic tumor (Table 5).[7]

Estrogen receptor positivity successfully predicts objective responses to hormonal therapy (Table 6) to the extent that only ER+ patients should be treated initially with ablation or hormone administration.[7,8] It is of interest that the perimenopausal patient, classically *not* responsive to hormonal therapy, tends to have lower ER positivity than either the premenopausal or postmenopausal (five years or more) patient. Clearly the traditional treatment decision based on premenopausal or postmenopausal status alone must be modified to include ER status.

TABLE 2
Results of Surgical Treatment Alone

	Ten-Year Treatment Failure Rate	Ten-Year Survival
Negative nodes	24%	65%
Positive nodes:		
1–3	65%	38%
4 or more	86%	13%
All	76%	25%
All patients	50%	46%

(Note: Adapted from the first NSABP Protocol) **(By Permission)**

TABLE 3
Objective Response to Endocrine Therapy

	No. Responding/ No. Evaluable	% Response
Estrogen-Receptor Negative/ Progesterone-Receptor Negative	9/63	14%
Estrogen-Receptor Positive/ Progesterone-Receptor Positive	67/91	74%

(*Note:* Adapted from McGuire WL: Hormone receptors: Their role in predicting prognosis and response to endocrine therapy. *Semin Oncol* 5: 428–433, 1978) **(By Permission)**

Chemotherapy of Advanced Breast Cancer

A large number of chemotherapeutic drugs have been shown to produce objective responses defined as partial and complete responses (Table 7). Table 8 lists a number of the commonly used agents and responses. The early studies of Greenspan and others suggested that combination therapy was considerably more effective, and therefore the initial chemotherapeutic treatment is almost always a combination, most commonly Cytoxan-Methotrexate-5-fluorouracil (CMF). The CMF combination shown in Table 9 is based on an Eastern Cooperative Oncology Group (ECOG) protocol with 49/93 patients responding. Complete responses lasted a median of eight or more months, partial responses four to eight months. Many oncologists, including myself, use less Methotrexate, 30–40 mgm/M^2, and one series

TABLE 4
Estrogen Receptor and the Prognosis for Early Recurrence of Breast Cancer

Category	Recurrence at 18 months (%) Estrogen-Receptor Negative	Estrogen-Receptor Positive
Age:		
Less than 50	34	14
Over 50	35	8
Nodes involved:		
0	12	6.5
1–3	38	12.5
4 or more	62	27.0
Size of primary:		
Less than 2 cm	33	0
Greater than 2 cm	31	14

(*Note:* Adapted from Table 1, McGuire WL: *Semin Oncol* 5: 428, 1978, and Knight WA, et al: *Cancer Res* 37: 4669, 1977.) **(By Permission)**

TABLE 5
Distribution of Estrogen Receptor in Primary and Metastatic Breast Cancer

	Primary Biopsy		Metastatic Biopsy	
Age:	Under 50	50 or over	Under 50	50 or over
ER level:				
Under 3	37%	23%	52%	31%
3–10	20%	15%	14%	16%
11–100	41%	36%	29%	27%
101–2000	2%	20%	5%	20%

(*Note*: Taken from Table 2, McGuire WL: *Semin Oncol* 5: 429, 1978.) **(By Permission)**

showed a 62% response rate with CMF using Methotrexate at 40 mgm/M^2.

There is no doubt that the single most effective drug is doxorubicin hydrochloride (Adriamycin$^{(R)}$) with reported response rates of up to 45%. Combinations using Adriamycin also show a higher response rate than CMF or CMFP (See Table 9), and some oncologists use CAF as the initial treatment. It is, however, desirable to have a combination available for use after the initial treatment fails, and we have tended to reserve Adriamycin for use in relapse, usually combining it with the vinca alkaloid, vincristine.[4] An exception to this sequence is the premenopausal, ER– patient with extensive visceral and bone disease. These women usually have very rapid, progressive disease, and initial treatment with CAF is warranted in an attempt to obtain even a small measure of control of their disease.

An additional consideration is the treatment of the ER+ patient with combined hormonal and chemical therapy. Only some 10–20% of objective responses are complete responses, but patients achieving complete responses tend to have longer remissions and better survival. Moreover, a small number may be curable since the achievement of complete response in large numbers of patients has been associated historically with the development of very long-term survival or cure. Thus attempts to increase the number of patients achieving complete response and to maintain those in complete response for as long as possible are now the subject of intense study.

Legha and his colleagues at the M. D. Anderson Hospital and Tumor Institute recently reported on 116 patients with breast cancer achieving complete remission. A marked improvement in the number in complete response and the duration of complete response was seen in premenopausal patients who underwent

TABLE 6
Objective Response by Therapy and Estrogen Receptor

Therapy	Objective Response/Evaluable Patients		
	ER+ #%	ER– #%	Pre-ER patients (All comers)
Ablative Surgery:			
Adrenalectomy	40/76 (53%)	4/41 (10%)	28%
Oophorectomy	28/43 (65%)	2/74 (3%)	29%
Hypophysectomy	9/14 (64%)	0/12 (0%)	33%
Total	77/133(58%)	6/127(5%)	
Hormonal Therapy:			
Androgens	10/28 (36%)	2/22 (9%)	18%
Estrogens	38/60 (63%)	2/49 (4%)	36%
Glucocorticoid	15/32 (47%)	0/19 (0%)	29%
Total	63/120(53%)	4/90 (4%)	
Antiestrogens:			
Nafoxidine	12/17 (71%)	0/16 (0%)	
Tamoxifen	18/40 (45%)	0/15 (0%)	
Total	30/57 (53%)	0/31 (0%)	33%

(*Note:* Adapted from Table 2, Legha SS et al: *Ann Intern Med* 88: 69, 1978, and Table 4, Carbone PP, Davis TE: *Semin Oncol* 5: 417, 1978.) **(By Permission)**

TABLE 7
Tumor Response

Complete Remission	No clinical evidence of active tumor; no subjective evidence of disease
Complete Response	All measurable disease disappears
Partial Response	50% or greater reduction in measurable tumor in the absence of progression or recurrence of new lesions elsewhere
Stable Disease	Steady state or response less than 50% reduction in measurable tumor. No increase in size of any lesion or appearance of new lesions
Progressive Disease	Occurrence of any new lesion or increase of any measurable lesion > 50%, even in the face of regressing lesions elsewhere

(*Note:* Adapted from Carter SK: The design of clinical trials in cancer therapy (ed. M Staquet) Brussels: Éditions Scientifiques Européennes, 1972.) **(By Permission)**

oophorectomy and received chemotherapy immediately compared to women receiving chemotherapy when disease progression occurred.[9]

An earlier study of adrenalectomy, oophorectomy and chemotherapy by Hoge et al revealed a much higher objective response rate (80%) when compared to chemotherapy or hormonal ablation alone.[10] These and other studies suggest that attempts to increase the number of patients in complete response by combined therapy may be worthwhile. However, such studies remain research protocols, and much longer observation will be necessary to assess their true value.

Adjuvant Chemotherapy

The large number of patients failing to achieve cure following radical mastectomy sug-

TABLE 8
Summary of Single Agents Active Against Advanced Breast Cancer

Drug	No. Evaluable Patients	No. Objective Responses	Response (%)
Alkylating agents:			
Cyclophosphamide	529	182	34
Nitrogen mustard	92	32	35
Phenylalanine mustard	86	20	23
Chlorambucil	54	11	20
Thio-TEPA	162	48	30
Antimetabolites:			
5-Fluorouracil	1263	324	26
Methotrexate	356	120	34
6-Mercaptopurine	45	6	13
Arabinosyl cytosine	64	6	9
Vinca Alkaloids:			
Vincristine	226	47	21
Vinblastine	95	19	20
Antibiotics:			
Actinomycin D	44	5	11
Adriamycin	193	67	35
Bleomycin	8	0	0
Mithramycin	32	5	16
Mitomycin	60	23	38
Miscellaneous agents:			
Hydroxyurea	21	4	19
BCNU	76	16	21
CCNU	155	18	12
Methyl CCNU	33	2	6
Hexamethylmelamine	39	11	28
Imidazole carboxamide	29	2	7
Procarbazine	21	1	5

(*Note:* Compiled by Susan J. Mellette, MD, Professor of Medicine, Medical College of Virginia.)

TABLE 9
Useful Drug Combinations in the Treatment of Breast Cancer

Regimen	Drug Dosage and Schedule	Response Rate (%)
CMFVP	Cyclophosphamide 80 mg/m^2 p.o. daily	62
	Methotrexate 20 mg/m^2 i.v. weekly	
	Fluorouracil 500 mg/m^{2}i.v. weekly	
	Vincristine 1.0 mg/m^2 p.o. daily × 15 (then taper)	
CMF	Cyclophosphamide 100 mg/m^2 p.o. days 1–14	53
	Methotrexate 60 mg/m^2 i.v. days 1 & 8	
	5-Fluorouracil 600 mg/m^2 i.v. days 1 & 8	
	(repeat cycles every 4 weeks)	
CMFP	Cyclophosphamide 100 mg/m^2 p.o. days 1–14	63
	Methotrexate 60 mg/m^2 i.v. days 1 & 8	
	5-Fluorouracil 600 mg/m^2 i.v. days 1 & 8	
	Prednisone 40 mg/m^2 p.o. days 1–14	
	(repeat cycles every 4 weeks)	
AV	Adriamycin 75 mg/m^2 i.v. day 1	52
	Vincristine 1.4 mg/m^2 i.v. day 1 & 8	
	(repeat cycles every 3 weeks)	
CA	Cyclophosphamide 200 mg/m^2 p.o. days 3–6	74
	Adriamycin 40 mg/m^2 i.v. day 1	
	(repeat cycles every 3–4 weeks)	
CAF	Cyclophosphamide 100 mg/m^2 p.o. days 1–14	82
	Adriamycin 30 mg/m^2 i.v. days 1 & 8	
	Fluorouracil 500 mg/m^2 i.v. days 1 & 8	
	(repeat cycles every 4 weeks)	
DAV	Dibromodulcitol 150 mg/m^2 p.o. days 1–10	71
	Adriamycin 45 mg/m^2 i.v. day 1	
	Vincristine 1.2 mg/m^2 i.v. day 1	
	(repeat cycles every 4 weeks)	

(*Note*: From Table 3. Carbone PP, Davis TE: *Semin Oncol* 5:417, 1978.) **(By Permission)**

gests that breast cancer is in fact a systemic disease at a very early stage, if not at its onset. There is increasing evidence to support a multicentric origin for many tumors including breast cancer, and it is now apparent that very large numbers of cells are shed systemically by even small cancers. Moreover, surgical failure results in local recurrence in only about 15% of cases, and most of these patients eventually show dissemination at other sites.[4] Adjuvant chemotherapy given after surgery is designed to destroy disseminated tumor cells and increase the likelihood of cure.

Two major groups have studies in progress: the National Surgical Adjuvant Breast Project (NSABP) and the National Tumor Institute in Milan.[11,12,13] The initial NSABP trial used a single drug, L-phenylalanine mustard, and the first Milan study used CMF for 12 cycles. Benefit was seen in premenopausal patients with one to three nodes involved in both series and for four or more nodes in the Milan series. Tables 10A and 10B show data updated to four years as of May 1978 and represent the most recent comparative data. No benefit to premenopausal women without nodal involvement has been demonstrated. The situation for postmenopausal women is less certain at present because the Milan study is reported to show benefit for the woman with four or more nodes who is able to take 85% or more of the scheduled adjuvant chemotherapy.[13] The NSABP data do not show benefit. Therefore adjuvant therapy should be reserved for premenopausal women with one or more positive axillary nodes. To date, a clear-cut advantage for three drugs and for the duration of treatment has not been established, although treatment for six months and 12 months does not appear much different at the present.[14]

Antiestrogens

A number of steroidal and non-steroidal compounds have antiestrogenic effects. Most clinical trials have employed the nonsteroidal compounds nafoxidine and tamoxifen. The lat-

TABLE 10

A. Comparison of NSABP/Milan Data -Control Patients-

Age/ Menopause	Positive Nodes	% Disease Free at Four Years	
		NSABP	Milan
All Pts.	All	51	47
All Pts.	1–3	63	54
All Pts.	4	40	32
49/Pre-	All	43	41
50/Post-	All	56	52
49/Pre-	1–3	54	49
49/Pre-	4	35	23
50/Post-	1–3	67	58
50/Post-	4	43	42
		5/78	

B. Comparison of NSABP/Milan Data -Treated Patients-

Age/ Menopause	Positive Nodes	% Disease Free at Four Years	
		NSABP	Milan
All Pts.	All	59	66
All Pts.	1–3	74	74
All Pts.	4	40	49
49/Pre-	All	65	75
50/Post-	All	56	56
49/Pre-	1–3	86	87
49/Pre-	4	40	51
50/Post-	1–3	68	61
50/Post-	4	40	45
		5/78	

(*Note*: Courtesy of Dr. Bernard Fisher and the National Surgical Adjuvant Breast Project.)

ter is commercially available and is believed to bind to the estrogen receptor in the cytosol, translocate to the nucleus, and bind to chromatin but not release easily. Cytoplasmic receptors also are depleted after tamoxifen therapy. It is clear that the effectiveness of antiestrogenic treatment correlates very well with estrogen-receptor positivity. An overall response rate of about 33% is seen, but the rate in ER+, postmenopausal patients is as high as 60%.[15] This is similar to the percentage of tamoxifen response in patients previously responding to hormonal therapy. Patients failing to respond to hormonal therapy usually do not respond to tamoxifen.

Most studies have been done in postmenopausal patients, but benefit in premenopausal patients has not been excluded. The dose is 10 mgm by mouth twice a day and is usually tolerated well. Nausea and vomiting are seen in some patients (12% in one series), hot flushes in about 21%, hypercalcemia occasionally, and mild platelet count depression rarely.

Synthesis

The management of the patient with breast cancer increasingly depends on careful staging taking into account the major prognostic features outlined above. The patient with localized disease, small primary and no axillary nodes is probably best served at present by modified radical mastectomy or radical mastectomy, although studies in progress at a large number of centers are beginning to suggest that less extensive surgery with radiation therapy to the chest wall and nodes may be useful in *selected cases*. Knowledge of the presence or absence of axillary node metastasis and the number of nodes involved is of such central importance to prognosis that procedures which do not provide this information cannot be considered useful at this time.

Premenopausal patients with one or more positive nodes but without evidence of metastatic disease elsewhere should be considered candidates for adjuvant therapy. However, the question of whether adjuvant cytotoxic chemotherapy, immunotherapy, or hormonal therapy should be given and for how long remains in the investigative stage. Adjuvant chemotherapy with CMF cannot be considered of proven value for the general population of patients, and every effort should be made to include these patients in clinical trials to establish the value of adjuvant therapy.

The choice of therapy for the patient with extensive disease also has become more complex. ER+ patients of advanced age with cutaneous, pleural, nodal, early bone, or nodular pulmonary disease may respond well to estrogen administration, and on re-exacerbation, androgen or prednisone. Approximately 25% of these patients will show regression of the tumor when estrogen is stopped—the "rebound" phenomenon, which has also been described after androgen and tamoxifen therapy.

The premenopausal, ER+ patient currently is treated with oophorectomy initially and,

TABLE 11
Metastatic Disease

Premenopausal			Postmenopausal		
ER+	ER−		ER−	ER+	
Oophorectomy		Chemotherapy		Estrogen	
Medical adrenalectomy				Estrogen rebound	
Surgical adrenalectomy				Androgen	
Antiestrogen				Androgen rebound	
Chemotherapy				Antiestrogen	
				Progesterone or Corticosteroid	
				Chemotherapy	

upon relapse, adrenalectomy or hypophysectomy. In a series studied at the Medical College of Virginia,[16] medical adrenalectomy with aminoglutethimide and dexamethasone is almost as effective as surgical adrenalectomy and does not preclude a response to surgical adrenalectomy when tumor again progresses. A schematic flow sheet to indicate serial treatment measures for advanced disease is shown in Table 11.

The presence of extensive long bone metastases or vertebral destruction should be handled with radiotherapy to as small an area as possible. Some cases may require prophylatic internal fixation of the femur or humerus. Prompt laminectomy and decompression of the spinal cord in epidural tumors or vertebral collapse is always worthwhile. Chemotherapy rather than hormonal therapy will almost always be required in such cases because of the need for rapid control of the disease to ensure continued ambulation.

CNS involvement can frequently be handled with moderate doses of radiation to the whole brain (3000 rads in 10 fractions), but meningeal involvement may also require intrathecal Methotrexate administration.

Liver metastases, extensive visceral involvement, bone marrow, or interstitial pulmonary involvement present almost insurmountable management problems. However, some patients with liver metastases and marked liver dysfunction respond to cytotoxic drugs and these should be instituted. When the situation is desperate, doxorubicin containing regimens with their higher initial response rate are the current choice. Extensive involvement of more than one organ requires cytotoxic drugs for systemic effect and radiation of painful or obstructing masses of tumor.

Corticosteroids provide some short-term palliation of the patient with interstitial pulmonary involvement. When bone marrow involvement with persistent low blood counts precludes full doses of multiple drugs administered on the usual time schedules, reduction of doses and/or the number of drugs may still provide some means of control.

Some general tenets of management of the patient with breast cancer are summarized in Table 12. In all cases the most critical aspect of management is the close support of the patient by an understanding and sympathetic physician.

TABLE 12
Tenets of Breast Cancer Management

1. Make long-term plans for the management of the patient at the onset.
2. Preserve or restore mobility and CNS function.
3. Treatment of painful lesions is virtually always of benefit.
4. Start treatment for local recurrences or systemic disease early; do not delay.
5. Neither despair nor hold out unrealistic promise of cure. Hope is warranted by the facts.

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