Drug Therapy

TREATMENT OF BREAST CANCER

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BREAST cancer is a major public health problem worldwide. Management of breast cancer was last reviewed in the *Journal* in 1992.[1] The accumulation of new biologic information, the results of recent clinical trials, and the availability of new diagnostic and therapeutic tools make it appropriate to review the subject again.

EPIDEMIOLOGY

The incidence of breast cancer in the United States has been increasing gradually for the past three decades.[2,3] It was estimated that 181,600 new cases of breast cancer were diagnosed in the United States in 1997 and that 44,190 people would die of breast cancer during the same year. However, incidence and mortality have recently leveled off and even decreased slightly.[3] Similar decreases in mortality were recently reported in Sweden and the United Kingdom.[4,5]

The incidence of breast cancer increases with age, although the rate of increase slows after menopause.[6,7] Early menarche, late menopause, and nulliparity increase the risk of breast cancer. Atypical lobular or ductal hyperplasia also increases the risk, and benign breast disease does so marginally.[8,9] Other risk factors are early exposure to ionizing radiation, long-term postmenopausal estrogen-replacement therapy, and alcohol consumption. The most important risk factor is a family history of breast cancer.[10-13] About 5 to 10 percent of all breast cancers occur in high-risk families, and there are several familial breast cancer syndromes, including the breast–ovarian cancer syndrome, the Li–Fraumeni syndrome, and Cowden's disease.[12]

BIOLOGY

The recent identification and cloning of *BRCA1* and *BRCA2* has expanded our knowledge of familial breast cancer.[14,15] Germ-line mutations in these two genes are associated with a 50 to 85 percent lifetime risk of breast cancer, ovarian cancer, or both. Tests for these mutations exist, and research efforts to develop comprehensive genetic screening and counseling programs are ongoing.[16] All breast cancers have somatic genetic abnormalities. In sporadic breast cancer, abnormalities have been identified in several genes (including *p53, bcl-*2, c-*myc,* and c-*myb*),[17,18] and in some cancers normal genes or gene products (HER-2/*neu* and cyclin D1) are overexpressed. However, the number and types of mutations necessary for the development of sporadic breast cancer are not known.

Many factors that stimulate or inhibit growth influence the growth and proliferation of breast-cancer cells.[19] Gonadal steroid hormones (estrogens, progestins, and androgens), growth factors (epidermal growth factor, transforming growth factors α and β, and insulin-like growth factors I and II), and various cytokines and lymphokines influence the behavior and phenotypic expression of breast cells. For instance, production of parathyroid hormone–related protein, prostaglandin E, or interleukin-6 by the tumor leads to the development of osseous metastases.[20] The recognition that these factors influence the growth and dissemination of breast cancer has provided new targets for therapeutic and preventive intervention.[21-23] Breast cancer also induces neovascularization, which, in turn, facilitates the metastatic process.[23] Metastatic spread is not a random mechanical phenomenon but requires systematic interaction among breast cells, stroma, and surrounding normal tissue at both primary and metastatic sites.[24] Adhesion molecules, local mediators, hormones, and growth factors must all act for metastases to develop. On the basis of this new information, diagnosis and treatment have changed. Many new cytotoxic and hormonal agents have emerged from new biologic concepts and are being developed for clinical use.

DIAGNOSTIC APPROACHES

Systematic screening by means of mammography and clinical examination results in early diagnosis of breast cancer and a 25 to 30 percent decrease in mortality due to breast cancer in women over the age of 50 years (Table 1)[25] and probably also in women between the ages of 40 and 50 years.[26] The American Cancer Society and the National Cancer Institute recommend annual screening mammography for women older than 40 years who have a standard risk of breast cancer.[26,27] In women from high-risk families,

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TABLE 1. BENEFIT OF SCREENING MAMMOGRAPHY
ACCORDING TO AGE.*

STUDY	DURATION OF FOLLOW-UP	SCREENING INTERVAL	RELATIVE RISK OF DEATH FROM CANCER (95% CI)†	
			AGE 50–74 YR	AGE 40–49 YR
	yr	mo		
Edinburgh	10	24	0.8 (0.6–1.1)	0.8 (0.5–1.5)
Malmö	12	18–24	0.9 (0.6–1.2)	0.5 (0.2–1.2)
Kopparberg	12	24–33	0.8 (0.5–0.9)	0.8 (0.4–1.4)
Östergotland	12	24–33	0.8 (0.6–1.0)	1.3 (0.8–2.3)
Canada	7	12	1.0 (0.6–1.5)	1.4 (0.8–2.2)
Health Insurance Plan	10	12	0.7 (0.5–1.0)	0.8 (0.5–1.2)
Stockholm	8	28	0.6 (0.4–1.1)	1.0 (0.5–2.0)
Gothenburg	7	18	0.9 (0.5–1.6)	0.7 (0.3–2.0)
Overall	—	—	0.8 (0.7–0.9)	0.9 (0.8–1.1)

*Data are modified from Tables 2 and 3 in Kerlikowske et al.,[25] with the permission of the publisher.

†Relative risks are for women who underwent mammographic screening as compared with those who did not. CI denotes confidence interval.

especially those with *BRCA1* or *BRCA2* mutations, screening should start at 25 years of age, or 5 years earlier than the earliest age at which breast cancer was diagnosed in a family member. Substantial technical improvements have been made in screening mammography, and additional improvements are expected to result from digital mammography. Breast magnetic resonance imaging and technetium-99m sestamibi imaging are under evaluation and may further increase our capability for early diagnosis.[28,29]

Twenty years ago, incisional or excisional biopsies were the standard methods for confirming the diagnosis; today, fine-needle aspiration[30] or core needle biopsy[31] is the standard. Ultrasound-guided core needle biopsy, stereotactic biopsy,[32] and magnetic resonance–directed biopsy have become important diagnostic tools, especially for women with suspicious but nonpalpable breast masses. The use of large-core needle-biopsy techniques increases the pathologist's ability to characterize the lesion.[33]

THERAPY

Primary Breast Cancer

In some women breast cancer is a local disease without distant spread. Such early breast cancers are usually diagnosed by screening mammography and are highly curable with local or regional treatment alone.[34] However, most women with primary breast cancer have subclinical metastases, and in a high percentage of those treated with apparently curative surgery (with or without radiotherapy), distant metastases ultimately develop.[35,36]

Local and Regional Treatment

Radical mastectomy has been largely discontinued and is seldom, if ever, indicated today.[37] Randomized trials have established that for most women with early breast cancer, lumpectomy (wide excision of the tumor with preservation of the breast) with radiotherapy is the preferred treatment (Fig. 1),[38] and up to 50 percent of women with early breast cancer in the United States are now treated in this way. However, there are marked geographic variations in the use of this treatment in the United States,[39] suggesting that patients' preferences and physicians' choices often override medical criteria in the selection of treatment. Radiotherapy, an integral part of breast-conserving treatment, is inappropriately withheld from some women, especially those older than 65 years.[40] Noninvasive (in situ) ductal and lobular breast cancer can also be treated adequately with lumpectomy and radiotherapy.[41,42]

Axillary Lymph-Node Dissection

The probability of recurrence is higher for women with histologically positive axillary lymph nodes and increases with each additional positive node. Axillary lymph-node dissection provides prognostic information but has minimal therapeutic benefit or none, especially in women with clinically negative axillary lymph nodes,[43] and it is responsible for most of the morbidity associated with breast surgery. Therefore, there is increasing interest in developing alternative methods to obtain prognostic information. Sentinel-lymph-node mapping is a procedure in which a radioactive substance or a blue dye is injected into the area around the tumor; a short time later, the lower ipsilateral axilla is explored through a small incision and the lymph node that has taken up the dye or radioactive substance (i.e., the sentinel node) is excised.[44] If it is histologically negative, the rest of the axillary lymph nodes are also likely to be negative. In expert hands, this procedure identifies the sentinel node in more than 90 percent of women. Elsewhere in this issue of the *Journal*, Krag et al. report similar results in a large multicenter trial.[45] The positive predictive value of a successful sentinel-node biopsy approaches 100 percent, whereas its negative predictive value exceeds 95 percent.[44,45] Many patients with clinically negative axillary lymph nodes could be spared an axillary dissection if the sentinel node was found to be negative.

An alternative approach is to analyze the primary tumor for nuclear or histologic grade, kinetics of cell growth and division, hormone-receptor expression, markers of invasive or metastatic capability, or blood-vessel content. A combination of these prognostic markers might provide an acceptable substitute for the information derived from axillary lymph-node examination. Until these newer techniques are vali-
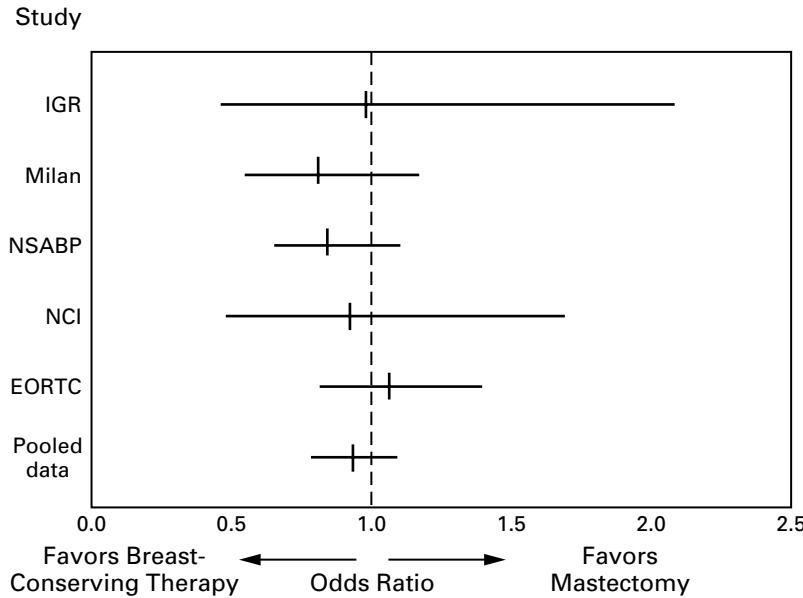
Study

Figure 1. Individual and Pooled Odds Ratios for Survival at 10 Years in Women with Breast Cancer Treated by Breast-Conserving Therapy as Compared with Mastectomy.

Breast-conserving therapy consisted of breast-conserving surgery plus radiation. The horizontal bars indicate 95 percent confidence intervals. For the pooled data, the odds ratio is 0.9 (95 percent confidence interval, 0.8 to 1.0). IGR denotes Institut Gustave–Roussy, NSABP National Surgical Adjuvant Breast and Bowel Project, NCI National Cancer Institute, and EORTC European Organization for Research and Treatment of Cancer. Adapted from Fisher,[35] with the permission of the publisher.

dated, axillary dissection remains the standard of care for all women with invasive breast cancer or large non-invasive tumors (>2.5 cm).

Radiotherapy

Radiotherapy is an integral part of breast-conserving treatment.[34,38] A recent randomized trial showed that administering chemotherapy before radiotherapy resulted in higher survival rates when both chemotherapy and radiotherapy were given postoperatively.[46]

Postmastectomy radiotherapy reduces the incidence of local and regional recurrences by 50 to 75 percent, but in most randomized trials, and according to a meta-analysis, this reduction was not accompanied by increased survival.[47-50] For that reason and because of its potential for long-term adverse effects, radiotherapy after mastectomy is indicated only for women at high risk for local or regional recurrence (patients with large tumors invading the skin of the breast or the chest wall or those with many positive axillary lymph nodes). However, in two recent, long-term randomized studies of high-risk premenopausal women with breast cancer treated with modern radiotherapy techniques and chemotherapy or with chemotherapy alone, there were fewer local and regional recurrences and overall survival was significantly better among the women treated with radiotherapy and chemotherapy (Table 2).[51,52] These results have renewed interest in postmastectomy radiotherapy.

TABLE 2. TEN-YEAR CANCER-FREE SURVIVAL AND OVERALL SURVIVAL AMONG WOMEN TREATED WITH CHEMOTHERAPY WITH OR WITHOUT RADIOTHERAPY AFTER MASTECTOMY.

STUDY AND OUTCOME	NO. OF SUBJECTS	PERCENT SURVIVING		P VALUE
		CHEMOTHERAPY	CHEMOTHERAPY AND RADIOTHERAPY	
British Columbia[51]	318			
Cancer-free survival		41	56	0.007
Overall survival		54	64	0.07
Danish Breast Cancer Cooperative Group[52]	1708			
Cancer-free survival		34	48	<0.001
Overall survival		45	54	<0.001

Systemic Hormone Therapy or Chemotherapy

The optimal treatment for women with primary breast cancer involves multiple methods and includes systemic therapy with hormonal agents, combination chemotherapy, or both. Over the past 25 years, various aspects of systemic therapy have been studied in many randomized trials, and there have been four overviews of data from the available randomized trials.[53-56] Current knowledge is based on about 400 trials including more than 220,000 women. Hormonal therapy and chemotherapy added to local

treatment favorably alter the natural history of breast cancer. The reduction in the rates of recurrence and death persists beyond 15 years for all forms of systemic treatment. Most women with primary breast cancer have sufficient residual risk after regional therapy to benefit from systemic therapy, but for some the benefit is marginal. The indications for systemic adjuvant therapy are shown in Table 3.

For adjuvant therapy, combination chemotherapy is more effective than single-drug therapy, reducing the annual risk of death by about 20 percent.[53] Although the effects of combination chemotherapy are more marked in women younger than 60 years, especially those who are premenopausal when therapy is begun, its effectiveness has been clearly demonstrated up to the age of 69 years. Adjuvant tamoxifen therapy significantly reduces the risks of recurrence and death in women in all age groups. The benefit is greater when tamoxifen is administered for about five years, rather than one to three years, and when it is given to women with estrogen-receptor–positive tumors.[54] Recent analyses suggest that women with estrogen-receptor–negative tumors should not be treated with hormonal therapy. Treatment for more than five years is no more effective than treatment for five years.[57]

Preoperative Chemotherapy

Chemotherapy is usually administered after surgery in women with operable breast cancer. However, for women with large operable tumors, preoperative chemotherapy may have some advantages. Several reports[53,58] have indicated that close to 90 percent of primary operable tumors decrease in size by more than 50 percent after chemotherapy, thus making lumpectomy a possibility for many women who would otherwise have required a mastectomy. In terms of survival, there is no apparent advantage to preoperative chemotherapy as compared with postoperative chemotherapy.

Duration of Chemotherapy

In several trials, combination treatment for less than three months was inferior to treatment for four to six months, whereas treatment with a single combination-chemotherapy regimen, such as cyclophosphamide, methotrexate, and fluorouracil (CMF), for longer than six months was no more effective than treatment for four to six months.[53,55,59] The combinations used most often are fluorouracil, doxorubicin, and cyclophosphamide (FAC); fluorouracil, epirubicin, and cyclophosphamide (FEC); doxorubicin and cyclophosphamide (AC); and CMF. These combinations are administered intermittently at intervals of three to four weeks. Six cycles of FAC or FEC (duration, 18 to 24 weeks), six cycles of CMF (duration, 18 to 24 weeks), or four cycles of AC (duration, 12 to 16 weeks) are considered standard therapy. A recent report of the preliminary results of a large randomized trial suggested that the addition of four cycles of paclitaxel (duration, 12 to 16 weeks) to four cycles of AC improved both disease-free survival and overall survival rates.[60] In premenopausal women, ovarian ablation has a substantial benefit, equivalent to that of combination chemotherapy or tamoxifen.[53,56] This benefit persists for 15 years after treatment.

Combination Chemotherapy and Hormone Therapy

The combination of tamoxifen (or ovarian ablation for premenopausal women) and chemotherapy is more effective than either alone.[53,55,56,59] Therefore,

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TABLE 3. INDICATIONS FOR ADJUVANT SYSTEMIC THERAPY AFTER SURGERY IN WOMEN WITH OPERABLE BREAST CANCER.

TYPE OF DISEASE	ADJUVANT THERAPY INDICATED*
Breast cancer without evidence of invasion	
Noninvasive breast cancer (ductal or lobular carcinoma in situ)	None
Breast cancer with evidence of invasion, but negative axillary lymph nodes	
Microinvasive breast cancer (<1 mm in largest diameter)	None
Invasive ductal or lobular carcinoma <1 cm in largest diameter	None
Invasive carcinoma <3 cm in largest diameter with favorable histologic findings (pure tubular, mucinous, or papillary)	None
Invasive ductal or lobular carcinoma ⩾1 cm in largest diameter	Chemotherapy, hormonal therapy, or both
Invasive carcinoma ⩾3 cm in largest diameter with favorable histologic findings (pure tubular, mucinous, or papillary)	Chemotherapy, hormonal therapy, or both
Invasive breast cancer with positive axillary lymph nodes	
All tumors, regardless of size or histologic findings	Chemotherapy, hormonal therapy, or both

*Chemotherapy consists of fluorouracil, doxorubicin, and cyclophosphamide (FAC); doxorubicin and cyclophosphamide (AC); or cyclophosphamide, methotrexate, and fluorouracil (CMF). Hormonal therapy consists of tamoxifen or ovarian ablation (either surgical or chemical).

the combination of chemotherapy and tamoxifen is recommended, especially for women with a high risk of recurrent disease. There is substantial agreement about the choice of optimal adjuvant therapy once it has been determined that a woman might benefit from this intervention (Table 4).

Dose-Intensive and High-Dose Chemotherapy Regimens

In dose-intensive regimens, chemotherapy is administered in conventional doses but at shorter intervals; in high-dose regimens, chemotherapy is given in doses higher than conventional doses. Although preliminary results with these regimens are encouraging, there is no evidence from randomized trials that either type of regimen is more effective than standard-dose adjuvant chemotherapy or than chemotherapy and hormonal therapy combined. Ongoing randomized trials should help to determine the efficacy of high-dose regimens and new therapeutic agents as curative treatments in breast cancer.[61,62]

Locally Advanced and Inflammatory Breast Cancer

Stage III breast cancer includes tumors larger than 5 cm in the largest diameter, tumors of any size with direct invasion of the skin of the breast or the chest wall, and any tumors with fixed or matted axillary lymphadenopathy. Women with stage III or locally advanced breast cancer should be treated with preoperative chemotherapy or hormonal therapy, surgery, and radiotherapy.[63,64] In more than 65 percent of such women, the tumors shrink by more than 50 percent with preoperative chemotherapy. Most previously inoperable tumors become operable, and some become amenable to breast-conserving therapy.[64] Limited data suggest that adjuvant chemotherapy and hormonal therapy are indicated after preoperative chemotherapy and regional treatment.[65] Excellent local control can be achieved in 80 to 90 percent of women, and about 30 percent of women with stage IIIB tumors (tumors with direct invasion of the skin of the breast or the chest wall) or inflammatory breast cancer remain free of cancer after 10 years.[63,66]

Metastatic Breast Cancer

The clinical course of metastatic breast cancer is variable; this heterogeneity results in large variations in growth rate and responsiveness to systemic therapy. Chemotherapy, hormonal therapy, radiotherapy, and limited surgery are all used in the treatment of women with metastatic breast cancer,[67] although the overwhelming majority of these women will die of their disease.[68] Therefore, optimal palliation and prolongation of life are the main goals of treatment. It is important to use all available treatments to obtain maximal control of symptoms, prevent serious complications, and prolong life with minimal disruption of the woman's lifestyle and quality of life (Fig. 2).

Diagnosis

Frequent testing to identify recurrences and metastases in order to institute aggressive treatment has not altered the clinical course of women with meta-

TABLE 4. SELECTION OF ADJUVANT SYSTEMIC THERAPY FOR WOMEN WITH OPERABLE PRIMARY BREAST CANCER AND INDICATIONS FOR ADJUVANT TREATMENT.

CHARACTERISTICS OF PATIENT AND TUMOR		LEVEL OF RISK	ADJUVANT SYSTEMIC THERAPY*
AGE	ESTROGEN-RECEPTOR STATUS		
<50 yr	Negative	Any	Chemotherapy
	Positive	Low	Hormonal therapy or Chemotherapy or Chemotherapy and hormonal therapy
	Positive	Moderate or high	Chemotherapy and hormonal therapy or Investigational therapies
	Unknown	Any	Chemotherapy and hormonal therapy
≥50 yr	Negative	Any	Chemotherapy
	Positive	Low	Tamoxifen or Chemotherapy and hormonal therapy
	Positive	Moderate or high	Chemotherapy and hormonal therapy or Investigational therapies
	Unknown	Any	Chemotherapy and hormonal therapy

*Chemotherapy consists of fluorouracil, doxorubicin, and cyclophosphamide (FAC); doxorubicin and cyclophosphamide (AC); or cyclophosphamide, methotrexate, and fluorouracil (CMF). Hormonal therapy consists of tamoxifen or ovarian ablation (either surgical or chemical).
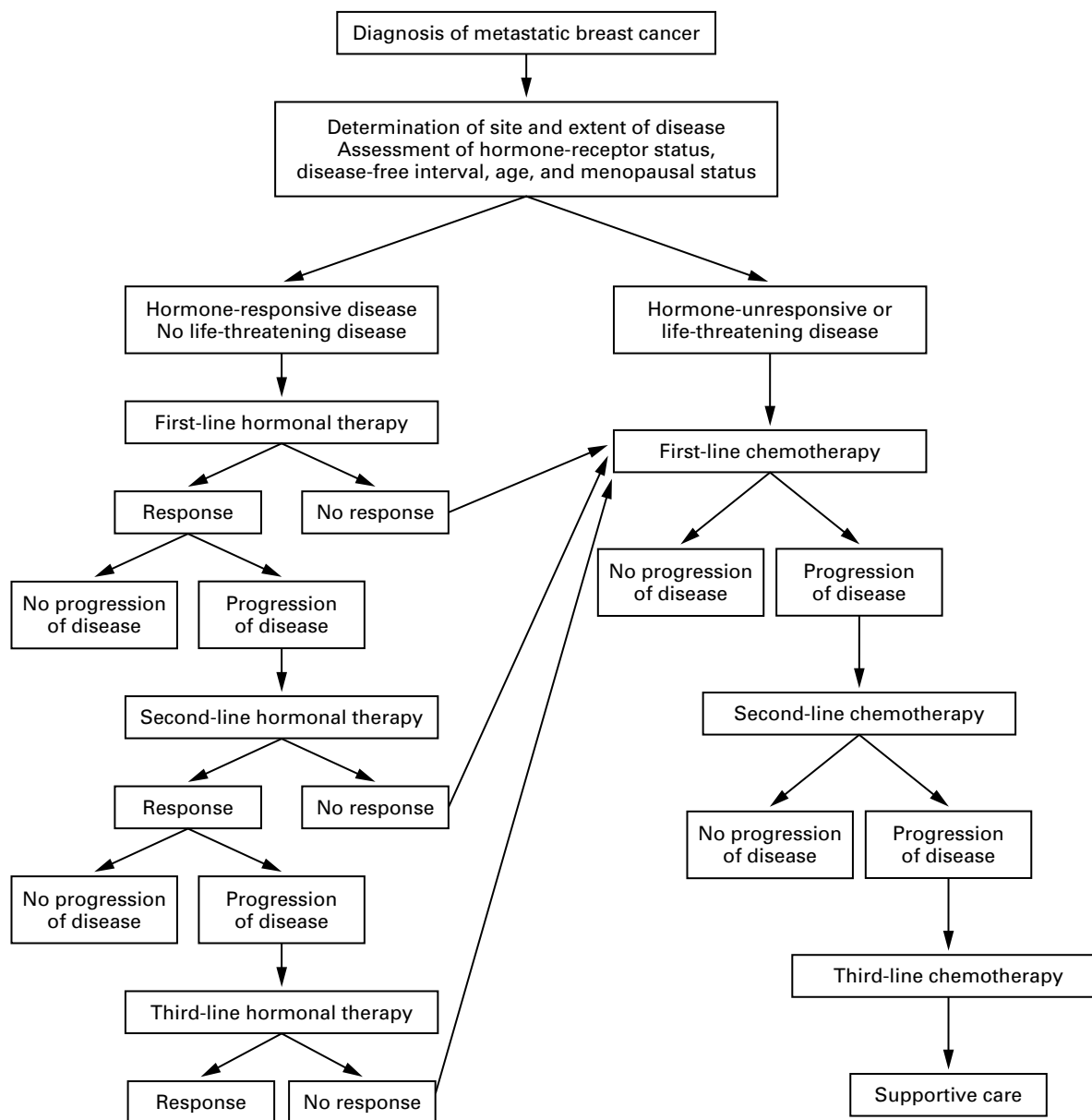
Figure 2. Optimal Palliative Therapy for Women with Metastatic Breast Cancer.

static breast cancer. Most recurrences or metastases are diagnosed on the basis of symptoms and physical findings, and extensive biochemical testing or imaging contributes little.[69,70] Guidelines for surveillance of asymptomatic women are shown in Table 5.[71]

Treatment

Once metastatic breast cancer becomes evident, it is appropriate to determine the extent and location of metastases. An overall therapeutic strategy is then developed on the basis of age, disease-free interval, hormone-receptor status, and extent of disease. For women with limited and non−life-threatening disease, especially those who have no symptoms, are elderly, or have estrogen-receptor−positive tumors, hormonal therapy is the initial treatment of choice (Fig. 2).[66,72] There has been a quiet revolution in hormonal therapy. Ablative endocrine procedures have been replaced by specific, well-tolerated hormonal treatments (antiestrogens, aromatase inhibitors, gonadotropin-releasing−hormone analogues, and progestins) (Table 6). Women who have a response to one hormonal intervention often have a response to a second after the first becomes ineffective.[72] Some women may thus

TABLE 5. GUIDELINES FOR SURVEILLANCE OF WOMEN WITH OPERABLE BREAST CANCER
AFTER THE COMPLETION OF PRIMARY TREATMENT.*

PROCEDURE	FREQUENCY
Education of patient about symptoms and signs of recurrence	At the completion of therapy and as needed
History and physical examination	Every 3 to 6 months for the first 3 years, every 6 to 12 months for the next 2 years, then annually
Breast self-examination	Monthly
Mammography	
Contralateral	Annually
Ipsilateral (remaining breast after lumpectomy)	Annually
Other recommended cancer-screening procedures†	Annually or every 2 years
Complete blood count, automated blood-chemistry studies, assays for serum tumor markers (carcino-embryonic antigen, CA2729, CA15-3)	Not recommended
Radionuclide bone scanning; imaging of the chest, abdomen, pelvis, or brain	Not recommended

*Guidelines are from the American Society of Clinical Oncology.[71]

†Other recommended procedures are pelvic examination with Pap smear, rectal examination, fecal occult-blood testing, and examination of the skin.

benefit from three or four hormonal therapies in sequence and have a good quality of life with minimal symptoms and side effects for several years. Twenty to 35 percent of women with metastatic breast cancer have an objective response to the initial hormonal therapy.[72,73] For second-line hormonal treatment of women with receptor-positive tumors, the probability of an objective response ranges from 10 percent to 20 percent,[74] and another 15 to 30 percent of women may have stable disease for six months or longer. Table 6 describes the preferred sequence of current hormonal options.

Eventually, in most women, metastatic breast cancer becomes refractory to hormonal treatment, at which time the women should receive chemotherapy (CMF or FAC). Fifty to 80 percent of women have an objective response to FAC, and 40 to 60 percent have an objective response to CMF.[75] Both regimens provide substantial palliation with tolerable levels of toxicity. In a recent meta-analysis of randomized trials, anthracycline-containing combinations were superior to CMF.[76] In the past 10 years, several new drugs have become available for the management of breast cancer (Table 7).[62,67] Among these, vinorelbine, a third-generation vinca alkaloid,[77] and the taxanes (paclitaxel and docetaxel)[78] are the most prominent. Vinorelbine, paclitaxel, and docetaxel given alone result in response rates similar to those associated with CMF as first-line treatment. Combinations of taxanes and anthracyclines result in responses in 40 to 94 percent of women in first-line treatment and complete remissions in 12 to 41 percent.[79] The durations of remission and times to progression after treatment with doxorubicin–paclitaxel or doxorubicin–docetaxel combinations are similar to those after therapy with CMF or FAC.

The approach to metastatic breast cancer that progresses after hormonal therapy followed by first-line chemotherapy is changing rapidly.[80-82] Today, the taxanes and vinorelbine are the second-line and third-line treatments of choice, respectively, and we know that taxane-containing salvage regimens improve overall survival.[81,82] Another area of progress has been the treatment of anthracycline-resistant breast cancer, defined as disease that progresses during treatment with a regimen containing an anthracycline (doxorubicin or a related drug). Before taxanes became available, the response rates in women with tumors resistant to anthracyclines (as second-line or third-line treatment) were less than 10 percent, and their overall survival was less than six months. Now, with the availability of taxanes, the response rates in these women range from 30 percent to 40 percent and survival for 10 to 12 months is customary.[81,83,84]

TABLE 6. HORMONAL THERAPIES FOR WOMEN WITH
METASTATIC BREAST CANCER.

ORDER OF THERAPY	PREMENOPAUSAL WOMEN	POSTMENOPAUSAL WOMEN
First line	Antiestrogens or ovarian ablation (chemical, surgical, or postradiation)	Antiestrogens
Second line	Ovarian ablation after antiestrogens; antiestrogens after ovarian ablation	Aromatase inhibitors
Third line	Progestins	Progestins
Fourth line	Androgens	Androgens or estrogens

TABLE 7. NEW AGENTS FOR SYSTEMIC THERAPY IN WOMEN
WITH METASTATIC BREAST CANCER.*

AGENT	STAGE OF CLINICAL DEVELOPMENT	RESPONSE RATE
		%
Hormonal		
Antiestrogens		19–54
Toremifene (Fareston)	Commercially available	
Raloxifene (Evista)	Approved by the FDA for osteoporosis; in phase 3 trials	
Idoxifene	In phase 3 trials for metastatic breast cancer	
Faslodex (ICI 182,780)	In phase 3 trials for metastatic breast cancer	
Aromatase inhibitors		12–39
Formestane	Commercially available in Europe	
Anastrozole (Arimidex)	Commercially available; in phase 3 trials	
Letrozole (Femara)	Commercially available; in phase 3 trials	
Vorozole	In phase 3 trials for metastatic breast cancer	
Exemestane	In phase 3 trials for metastatic breast cancer	
Cytotoxic		
Anthrapyrazoles		18–63
Losoxantrone	In phase 3 trials for metastatic breast cancer	
Anthracyclines		18–33
Liposomal doxorubicin (D 99)	In phase 3 trials for metastatic breast cancer	
Purine analogues		25–46
Gemcitabine (Gemzar)	Commercially available for pancreatic cancer; in phase 3 trials for metastatic breast cancer	
Taxanes		13–68
Docetaxel (Taxotere)	Commercially available; in phase 3 trials as adjuvant therapy and for metastatic breast cancer	
Paclitaxel (Taxol)	Commercially available; in phase 3 trials as adjuvant therapy and for metastatic breast cancer	
Thymidylate synthase inhibitors		20–36
Capecitabine	Commercially available; in phase 3 trials for metastatic breast cancer	
Raltitrexed (Tomudex)	In phase 3 trials for metastatic breast cancer	
UFT	In phase 3 trials for metastatic breast cancer	
Vinca alkaloids		18–52
Vinorelbine (Navelbine)	Commercially available for lung cancer; in phase 3 trials as adjuvant therapy and for metastatic breast cancer	

*FDA denotes Food and Drug Administration, and UFT uracil–ftorafur.

Bone is the most common site of metastases in breast cancer, and bone metastases are the cause of substantial morbidity and complications. Bisphosphonates (pamidronate and clodronate [clodronic acid]) added to chemotherapy or hormonal therapy reduce pain and the incidence of complications, and they prolong survival free of bone-related events.[85]

High-Dose Chemotherapy

The development of techniques to harvest, store, and reinfuse autologous hematopoietic stem cells and the availability of hematopoietic growth factors have allowed the evaluation of very-high-dose chemotherapeutic regimens (given at doses 2 to 20 times as high as standard doses).[86,87] Two types of high-dose regimens have been studied. In one, a single cycle of a high-dose combination of cytotoxic drugs (usually alkylating agents) is administered, which ablates the bone marrow. The purpose of treatment is not to destroy normal bone marrow, but to give the highest tolerable doses of chemotherapy in the hope of killing the highest possible number of breast-cancer cells.

Bone marrow damage is the earliest limiting toxic effect of most alkylating agents; this effect can be eliminated or lessened by harvesting autologous hematopoietic stem cells and reinfusing them after the administration of high-dose chemotherapy to repopulate normal bone marrow. In the second type of regimen, two to four cycles of cytotoxic-drug combinations are administered at doses that are higher than usual but do not ablate the bone marrow. These high-dose regimens result in higher overall rates of remission, and especially of complete remission (in the range of 40 to 60 percent), in women with previously untreated metastatic breast cancer, and 15 to 25 percent of women remain free of cancer for three to five years.[87-89] However, there is no evidence that such therapy results in any better palliation in women with refractory breast cancer than that obtained with standard-dose chemotherapy. In the absence of comparative trials, it is uncertain whether the 15 to 25 percent rate of long-term cancer-free survival is the result of high-dose therapy or simply a consequence of the selection of patients,[90] although in one small,

randomized trial, high-dose therapy resulted in better progression-free survival and overall survival than standard-dose therapy.[91]

CHEMOPREVENTION

The administration of adjuvant tamoxifen for five years after primary therapy reduces the incidence of contralateral breast cancer by 47 percent.[54] In a recently completed randomized study, more than 13,000 women at high risk for breast cancer received daily tamoxifen (20 mg) or placebo. After a mean follow-up of 3.5 years, there was a 45 percent decrease in the incidence of breast cancer in the tamoxifen group.[92] Endometrial cancer developed in twice as many women in the tamoxifen group as in the placebo group. There was also an increase in thromboembolic events in the tamoxifen group. These adverse effects occurred predominantly in women older than 50 years. Overall, the beneficial effects of tamoxifen outweighed its adverse effects. The results of two other studies of chemoprevention with tamoxifen and one of fenretinide are not yet available.

NOVEL THERAPIES

Cytotoxic agents under development include anthrapyrazoles,[93] liposomal anthracyclines,[94,95] gemcitabine,[96] several novel anti–folic acid compounds,[97] and new thymidylate synthase inhibitors.[98] Among the new hormonal agents, pure antiestrogens,[99] aromatase inhibitors (anastrozole, letrozole, and vorozole),[100] and selective estrogen-receptor modulators[101,102] are causing great excitement. One of the latter, raloxifene, approved for the treatment of osteoporosis, was associated with a reduction of more than 50 percent in the incidence of breast cancer in a recent randomized trial.[103]

An increased understanding of the biology of breast cancer has led to the identification of novel therapeutic targets. For example, the HER-2/*neu* oncogene is overexpressed in 20 to 30 percent of breast cancers, and these tumors are more aggressive and somewhat more resistant to chemotherapy than those not overexpressing the oncogene.[104] Thirteen percent of women with metastatic breast cancer overexpressing HER-2/*neu* had objective responses to weekly injections of monoclonal antibodies against the extracellular domain of the HER-2/*neu* oncoprotein.[105] When the antibody was administered with cisplatin, the overall response rate was 25 percent, and some of the responses lasted for more than one year. In a recently completed randomized trial in which chemotherapy was combined with the anti–HER-2/*neu* antibody, a doubling or tripling of the response rate, a prolongation of the time to disease progression, and increased overall survival were observed in patients who received the combination therapy as compared with those patients receiving chemotherapy alone.[106]

CONCLUSIONS

Marked progress has been made in the past 30 years in our understanding of breast cancer. The biologic behavior of this cancer, risk factors, and prognostic factors have been better characterized. We have identified several molecular genetic abnormalities that are associated with the development of invasive breast cancer and others that are correlated with its metastatic potential or response to treatment. The efficacy of our diagnostic and therapeutic approaches has improved, resulting in decreased mortality and in improved palliation for women for whom cure is not a possibility. Early diagnosis of primary breast cancer reduces the risk of death by 30 percent. Most patients with primary breast cancer can be optimally treated with breast-conserving local treatments, and the addition of systemic hormone therapy and chemotherapy reduces the risk of death by 25 to 50 percent. We have successfully taken the first steps in breast-cancer prevention and have developed several new drugs that are more effective and less toxic than the previous generation of antitumor agents.

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