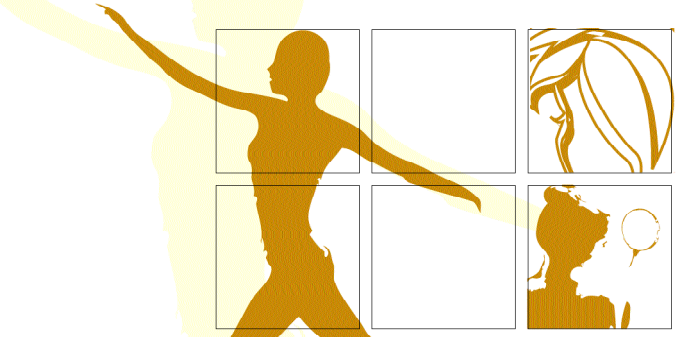

SYSTEMATIC THERAPY FOR BREAST CANCER

COREY J. LANGER, MD

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Systematic Therapy for Breast Cancer

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Introduction

Despite the rising breast cancer incidence in the United States (US), the death rate from it has been decreasing over the past decade.1,2 While some of the decrease in mortality can be attributed to a broader use of screening mammography, a significant portion of this is also due to the increased use of systemic therapies in the adjuvant setting. Identification of effective new agents for the treatment of metastatic disease has also resulted in prolonged survival and improved quality of life (QoL).

Hormonal Therapy for Breast Cancer

Several systemic strategies can be used to treat breast cancer. Over 100 years ago, Beatson demonstrated that advanced breast cancer could be managed by surgical oophorectomy. It is now clearly understood that the estrogen receptor (ER-alpha) is an important growth regulator of a significant number of breast cancers. About 60% of breast cancers express ER-alpha, and of those, nearly 60% will respond to strategies designed to interrupt ER-alpha function. More importantly, expression of ER-alpha serves as a predictive marker of patients who will respond to hormonal therapies.3

Currently, there are several ways to interrupt ER-alpha action. Tamoxifen was the first pharmacologic agent designed to target ER-alpha tumors in breast cancer.4 While an antiestrogen in the breast, tamoxifen can act as an estrogen agonist in some tissues. Selective estrogen receptor modulator (SERM) describes the drugs that bind directly to ER-alpha and affect its function.5 Toremifene and raloxifene target ER-alpha with both agonist and antagonist effects in different targets of estrogen action.6 A newer pure steroidal antiestrogen (fulvestrant) is currently in clinical trials and initial studies suggest that it will have good activity in breast cancer.7,8

In addition to directly blocking ER-alpha function by SERMs, diminishing serum estradiol levels has also been very effective in treating breast cancer in premenopausal women. In these women, interruption of ovarian function by luteinizing hormone-releasing hormone (LHRH) agonists can be used to perform a "medical oophorectomy." In postmenopausal women, inhibition of the peripheral conversion of estrogenic precursors (such as androstenedione) by selective aromatase inhibitors is highly effective for advanced breast cancer.

A variety of other hormonal agents such as medroxyprogesterone (a progestin) and fluoxymesterol (an androgen) also have activity in hormonal management of breast cancer. However, with the development of the newer agents, they have become third- and fourth-line strategies.

Chemotherapy for Breast Cancer

In women who have estrogen receptor negative (ER-) tumors, hormonal strategies are largely ineffective. However, a number of chemotherapeutic agents have been shown to have excellent activity in breast cancer.9 Many different classes of drugs (alkylators, antimetabolites, anthracycline antibiotics, tubulin-interacting agents, etc) have shown good activity as single agents. In addition, combination chemotherapy has become the mainstay of adjuvant chemotherapy for breast cancer.10

Targeted Therapy for Breast Cancer

Recognition of genes altered in breast cancer has led to the development of a new therapeutic class of agents specifically directed at a molecular target. Amplification of the c-erbB2/HER2 gene in some breast cancer tumors has enabled the design of a humanized monoclonal antibody (trastuzumab) directed against the HER2 protein.11 Trastuzumab, the first of a class of targeted therapies, has good single-agent activity in patients whose tumors overexpress the HER2 gene.12 In addition, trastuzumab, in combination with conventional cytotoxic chemotherapy, increases the response rate and duration of response compared with chemotherapy alone.13 Given the success of trastuzumab, additional targeted therapies directed against specific molecules and pathways (EGF AU:EGF=? receptor, angiogenesis, etc) will be forthcoming.

Adjuvant Therapy for Breast Cancer

Implementation of adjuvant therapy for breast cancer after surgical resection of the primary tumor and any involved lymph nodes has, in part, decreased the breast cancer mortality rate. Although a discussion of this complex topic is outside the scope of this review, the majority of breast cancer patients who have early stage disease will clearly benefit from some form of adjuvant therapy. Controversies on this topic were discussed at a National Institutes of Health consensus conference.10

For patients with estrogen receptor positive (ER+) tumors, 5 years of adjuvant therapy with tamoxifen improved overall survival in both lymph node positive and lymph node-negative patients.14 In premenopausal patients, use of tamoxifen or the LHRH agonist goserelin has also been shown to improve survival.15

At present, the place for the aromatase inhibitors in adjuvant therapy has not been established. A trial comparing tamoxifen, the aromatase inhibitor anastrozole, or tamoxifen and anastrozole together has completed accrual and results are expected soon.

Combination chemotherapy is also effective in resectable breast cancer. Most regimens involve a combination of at least two agents. Combinations of cyclophosphamide, methotrexate, and fluorouracil (CMF), doxorubicin and cyclophosphamide (AC), and cyclophosphamide, epirubicin, and fluorouracil (CEF) have all been shown to reduce mortality rates. While it appears that the anthracycline containing regimens showed a greater risk reduction than CMF when analyzed by meta-analysis, it is also clear that the benefit of AC over CMF is small.16 At present, the addition of a taxane to treatment with lymph node-positive breast cancer is controversial. While paclitaxel was approved by the US Food and Drug Administration (FDA) for use in lymph node-positive breast cancer patients, the initial positive study has not yet been published or confirmed by others.10 It is also not known if trastuzumab has a role in adjuvant therapy.17 Current clinical trials are addressing its use in combination with taxane chemotherapy.

Since all the adjuvant therapies provide only partial risk reduction (in general, about 20%–30% relative risk reduction) of recurrence and death, it is difficult to provide global recommendations for their use. Certainly, the absolute risk of recurrence for lymph node-positive patients warrants the institution of hormonal therapy, chemotherapy, or both. In lymph node-negative patients, it is worthwhile to consider the absolute risk of recurrence when making recommendations about adjuvant treatment. Tumor size, histologic features, the presence or absence of biomarkers, and the patient's general health status warrant consideration. Given the potential interaction of several factors, computer models that determine the absolute risk of recurrence and benefit of specific adjuvant therapies have been created.18,19

Treatment of Metastatic Disease

Once disease appears in a distant organ site, breast cancer is incurable and the goal of therapy should be palliation. Despite the lack of a curative program, both hormonal and cytotoxic therapies have the potential to improve survival and QoL.

In general, patients with ER+ tumors without life-threatening disease should be offered a trial of hormonal chemotherapy first. In patients who are both ER and progesterone receptor (PR) positive, a response rate of approximately 70% has been documented. PR is a better predictor of hormonal response than ER-alpha and ER-, PR+ patients have a good response to hormone therapy.3 Given the favorable toxicity profile and prolonged time to treatment progression, management of metastatic breast cancer with hormonal agents is one of the best options. Recent trials of the aromatase inhibitors versus tamoxifen have shown that the aromatase inhibitors are at least as good as tamoxifen, if not better.20–23 In premenopausal women, use of an ovarian ablation strategy, with or without tamoxifen or an aromatase inhibitor, can be highly effective.24 If an initial hormonal response can be demonstrated, then treatment with a second- and third-line hormonal agent can be effective.

In patients who have ER- or ER+ tumors and life-threatening disease, chemotherapy should be considered first. While hormonal agents can be highly effective, the response tends to be slower. Cytotoxic chemotherapy is more often associated with a rapid response rate. Thus, when an immediate response is desired, chemotherapy is an effective first strategy.

Many combination chemotherapy regimens have been tested in advanced breast cancer.25 In phase III studies, several combination regimens have higher activity than single agents. However, combination therapy also tends to cause more toxicity. Despite the desirability of a high response rate, the benefits of combination chemotherapy for palliation must be weighed against potential toxicity. It is also not clear whether survival is better prolonged by the use of sequential single agents or with combination chemotherapy.26 One example of this dilemma is when to incorporate trastuzumab into the therapeutic armamentarium. While trastuzumab alone has a 20%–30% response rate in HER2-amplified patients,12 the response rate for trastuzumab plus paclitaxel is about 70%.27 Can a patient initially be treated with trastuzumab and if the patient fails to respond, or progresses through single-agent trastuzumab, can paclitaxel be added at that point for additional benefit? Well-designed clinical trials are needed to address the true utility of combination chemotherapy versus sequential use of single agents.

In an attempt to maximize the clinical benefit of adjuvant chemotherapy, differing intensity and sequencing schedules have been explored. One of the first groups to explore the concept of dose intensity was the Milan group who added doxorubicin to their standard cyclophosphamide, methotrexate and fluorouracil (CMF) schedule. The chemotherapy was given sequentially, doxorubicin followed by CMF or alternating, with doxorubicin interspersed between the CMF courses. There was a statistically significant difference in the clinical benefit seen on the sequential arm, with a 10-year median follow-up, disease-free survival is 28% versus 42%.28

Other groups have tried dose intensification plus/minus increasing the total dose of
cyclophosphamide in an adjuvant setting in women with positive axillary nodes, the National Surgical Adjuvant Breast and Bowel Project's (NSABP) B-22 study failed to show a significant difference in disease-free or overall survival in any of the groups. The groups with intensified and/or increased cyclophosphamide had higher Grade IV toxicity.29 Currently there is no role for dose intensification outside a clinical study.

AC Versus CMF

Fisher et al reported on the NSABP's B-15 study, which compared 4 cycles of doxorubicin and adriamycin (AC), with 6 cycles of conventional CMF.30 There was no significant difference in disease-free or distant disease free survival. Regimen-related toxicity was comparable between the two regimens. There is also data to suggest a minor overall superiority for anthracycline-based regimens relative to CMF in HER-2 positive women.31 Cardiac toxicity remains a concern with an anthracycline based regimen, and even though cardiomyopathy and congestive heart failure are dose dependent, late effects of chemotherapy are another concern.32,33

CEF Versus CMF

Intensive cyclophosphamide, epirubicin, and fluorouracil (CEF) was compared with standard CMF (each given for 6 cycles) in node-positive breast cancer patients. With a median follow-up of 59 months, both the relapse-free survival and overall survival rates were superior in the CEF arm [53% vs 63% ($p=0.009$) and 70% versus 77% ($p=0.03$)], respectively.34

Ongoing studies are testing CEF versus AC versus AC followed by Paclitaxel. Other studies are ongoing testing AC followed by various combination of a taxane (either paclitaxel or docetaxel) plus/minus the addition of trastuzumab.

Common Breast Cancer Regimens

AC Regimen 01

AC: every 21 days (usually for 4 cycles)
Adriamycin (doxorubicin): 60 mg/m2 IV day
Cyclophosphamide: 600 mg/m2 IV day 1

AC=adriamycin cyclophosphamide
IV=intravenous

ACT Regimen 02

Adriamycin (doxorubicin): 60–90 mg/m2 IV day 1
Cyclophosphamide: 600 mg/m2 IV, repeat cycle every 21 days x 4 cycles **then**
Taxol (paclitaxel): 175 mg/m2 IV day 1, repeat every 21 days x 4 cycles

ACT=adriamycin cyclophosphamide taxol
IV=intravenous

ACT Regimen 03

AT: every 21 days
Adriamycin (doxorubicin): 50 mg/m2 IV day 1
Taxotere (docetaxel): 75 mg/m2 IV day 1

AT=adriamycin taxotere
IV=intravenous

CAF Regimen 04

Cyclophosphamide: 500 mg/m2 IV day 1
Adriamycin: 50 mg/m2 IV day 1
5-FU: 500 mg/m2 IV days 1 and 8 (FAC), repeat every 21 days

or

Cyclophosphamide: 100 mg/m2 PO days 1—14 or 600 mg/m2 IV day 1
Adriamycin (doxorubicin): 25 mg/m2 IV days 1 and 8 or 60 mg/m2 IV day 1
5-FU: 500–600 mg/m2 IV days 1 and 8; repeat every 28 days

CAF= cyclophosphamide adriamycin 5-fluorouracil
5-FU= 5-fluorouracil
IV= intravenous; AU: FAC=?

CMF Milan/Standard Regimen 05

CMF: every 28 days
Cyclophosphamide: 100 mg/m2 PO days 1–14
Methotrexate: 40 mg/m2 days 1 and 8
5-FU: 400–600 mg/m2 days 1 and 8

CMF=cyclophosphamide methotrexate 5-fluorouracil
5-FU=5-fluorouracil

CMF Regimen 06

CMF: every 28 days
Cyclophosphamide: 600 mg/m2 IV days 1 and 8
Methotrexate: 40 mg/m2 days 1 and 8
5-FU: 600 mg/m2 days 1 and 8

Bonnadona dose intense:
Adriamycin (Doxorubicin): 75 mg/m2 for 4 cycles
Followed by 6 cycles of standard CMF (see above)

CMF=cyclophosphamide methotrexate 5-fluorouracil
IV=intravenous
5-FU=5-fluorouracil

CEF-120 07

CEF-120: every 28 days for 6 cycles
Cyclophosphamide: 75 mg/m2 PO days 1–14
Epirubicin (ellence): 60 mg/m2 IV days 1 and 8
5-FU: 500 mg/m2 IV days 1 and 8

CEF-120=cyclophosphamide epirubicin 5-fluorouracil
5-FU=5-fluorouracil
IV=intravenous

FEC-200 Regimen

08

FEC-200: every 21 days for 6 cycles
5-FU: 500 mg/m2 IV
Epirubicin (ellence): 100 mg/m2 IV
Cyclophosphamide: 500 mg/m2 IV

FEC-200=5-fluorouracil epirubicin cyclophosphamide
5-FU=5-fluorouracil
IV=intravenous

AC f/b Taxol Regimen

09

Standard AC regimen (see above): for 4 cycles
followed by:
Taxol (paclitaxel): 135 mg/m2 IV every 3 weeks for 4 cycles

AC=adriamycin cyclophosphamide
AU: f/b=?
IV=intravenous

Chemotherapy Regimens

Anastrozole (Arimidex) 10

Mechanism of Action	Indications
Selective, nonsteroidal aromatase inhibitor, decreases estradiol concentrations (selectively inhibits conversion of androgens to estrogens).	First-line treatment of hormone receptor-positive or receptor-unknown locally advanced or metastatic breast cancer in postmenopausal women. Treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy.
Dose Range	**Side Effects**
1 mg PO QD (no requirement for mineral corticoid replacement therapy).	**AU:** ANY SIDE EFFECTS?

Capecitabine (Xeloda) 11

Mechanism of Action	Indications
Antimetabolite	Metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing regimen or resistant to paclitaxel and not candidates for further anthracycline therapy.
Dose Range	**Side Effects**
1,250 mg/m2 PO BID (total daily dose is 2,500 mg/mg2) at the end of a meal for 2 weeks followed by a 1 week rest period given as 3 week cycles.	Diarrhea common and dose limiting, nausea, vomiting, stomatitis, hematologic toxicity (especially lymphopenia), palmar-plantar erythrodysesthesia, dermatitis, and adverse hepatobiliary effects.

Capecitabine (Xeloda) 12

Mechanism of Action	Indications
Alkylating agent.	Adjuvant and metastatic breast cancer, used alone or in combination, and most often used in combination chemotherapy.
Dose Range	**Side Effects**
Various regimens (see common chemotherapy regimens section).	Hematologic toxicity, anorexia, nausea, vomiting, alopecia, hemorrhagic cystitis, and pulmonary and cardiac toxicity at high doses or with long-term therapy. Secondary malignancies have also been reported.

ARA-C (Cytosar, DepoCyt) 13

Mechanism of Action	Indications
Antimetabolite.	Intrathecal treatment of neoplastic meningitis from breast cancer.
Dose Range	**Side Effects**
Cytosar and others: 5–75 mg/m2 or 30–100 mg once every 2–7 days to once daily for 4 or 5 days. Cytarabine liposome injection (depoCyt): 50 mg/m2 every 2–4 weeks (see full dosing instructions for solid tumors).	Intrathecal administration rarely causes systemic toxicity. Most frequent effects are nau sea, vomiting, fever, and headaches.

ARA-C=cytarabine

Dextrazoxane (Zinecard) 14

Mechanism of Action	Indications
Chemoprotectant and cyclic EDTA derivative. Exact mechanism of action unknown, may chelate free iron and decrease hydroxy radical formation.	To prevent or reduce the incidence and severity of anthracycline-induced cardiomyopathy. Not recommended for use with initial doxorubicin therapy. Recommended for use in patients who have cumulative doxorubicin doses of 300 mg/m2.
Dose Range	**Side Effects**
Dose according to doxorubicin dose: dexrazoxane:doxorubicin is 10:1(600 mg/m2 dexrazoxane:60 mg/m2 doxorubicin)	AU: BLANK. ANY SIDE EFFECTS?

AU: EDTA=?

Docetaxel (Taxotere) 15

Mechanism of Action	Indications
Microtubule assembly stabilization.	Second-line therapy for locally advanced or metastatic breast cancer. Adjuvant therapy on clinical trials.
Dose Range	**Side Effects**
Premedication for hypersensitivity reactions and fluid retention: dexamethasone 8 mg PO BID for 3 days starting 1 day prior to docetaxel administration. (For every week administration, Dexamethasone course is often attenuated). 60–100 mg/m2 IV over 1 hour every 3 weeks. **Weekly dose:** 35 mg/m2 IV every week.	Hematologic toxicity (principally granulocytopenia), fever, hypersensitivity reactions, neurosensory defects (including paresthesia, dysethesia, pain), neuromotor toxicity, asthenia, alopecia, and fluid retention with peripheral edema and weight gain. GI side effects are usually mild to moderate.

IV=intravenous
GI=gastrointestinal

Doxorubicin (Adriamycin, others) 16

Mechanism of Action	Indications
Antineoplastic antibody; intercalating agent, free radical production, topoisomerase II inhibition.	Adjuvant and metastatic breast cancer.
Dose Range	**Side Effects**
Single agent: 60–75 mg/m2 IV x 1 dose, repeated every 3–4 weeks. **Combination regimens:** 40–60 mg/m2 IV x 1 dose, repeated every 3–4 weeks.	Hematologic toxicity (principally granulocytopenia, acute and chronic cardiac toxicity (see dosing instructions for cumulative doses 300 mg/m2), alopecia, stomatitis, and mucositis. Extravasation produces local necrosis.

IV=intravenous

Epirubicin (Ellence) 17

Mechanism of Action	Indications
Antineoplastic antibody; intercalating agent, free radical production, topoisomerase II inhibition.	Adjuvant therapy of breast cancer in patients with evidence of auxillary-node positivity.
Dose Range	**Side Effects**
CEF-120 dose range: every 28 days for 6 cycles. Cyclophosphamide: 75 mg/m2 PO days 1–14. Epirubicin (ellence): 60 mg/m2 IV days 1 and 8. 5-FU: 500 mg/m2 IV, days 1 and 8. **FEC-200 dose range:** every 21 days for 6 cycles. 5-FU: 500 mg/m2 IV. Epirubicin (ellence): 100 mg/m2 IV Cyclophosphamide: 500 mg/m2 IV	Hematologic toxicity (principally granulocytopenia, acute and chronic cardiac toxicity (see dosing instructions for cumulative doses 300 mg/m2), alopecia, stomatitis, and mucositis. Extravasation produces local necrosis.

Exemestane (Aromasin) 18

Mechanism of Action	Indications
Irreversible steroidal aromatase structurally related to the natural substrate androstendione.	Treatment of advanced breast cancer.
Dose Range	**Side Effects**
25 mg PO QD after a meal.	May cause fetal harm (indicated for use in postmenopausal women), hot flashes, nausea, fatigue, increased appetite, and weight gain.

5-FU 19

Mechanism of Action	Indications
Fluorinated pyrimidine antagonist. Antimetabolite.	Adjuvant and metatstatic breast cancer.
Dose Range	**Side Effects**
Usually used in combination regimens, see common breast cancer protocols.	Anorexia, nausea, vomiting, stomatitis, diarrhea, hematologic toxicity, alopecia, pruritic maculopapular rash, and palmar-plantar erythrodysethesia.

5-FU=5-fluoruracil

Gemicitabine (Gemzar) 20

Mechanism of Action	Indications
Synthetic pyrimidine nucleoside. Antimetabolite.	Metastatic breast cancer as 3rd- and/or 4th-line therapy.
Dose Range	**Side Effects**
Cycles usually done weekly for 3 consecutive weeks out of 4 with a range of 800–1200 mg/m2 IV weekly.	Hematologic toxicity and potent radiosensitizer in vitro. Hemolytic uremic syndrome has also been reported.

IV=intravenous

Goserelin Acetate Implant (Zoladex) 21

Mechanism of Action	Indications
LHRH agonist	Metastatic breast cancer in pre- and perimenopausal women.
Dose Range	**Side Effects**
3.6 mg subcutaneously every 4 weeks.	AU: BLANK. ANY SIDE EFFECTS?

LHRH=lutenizing hormone-releasing hormone

Letrozole (Femara) 22

Mechanism of Action	Indications
Selective, nonsteroidal aromatase inhibitor that decreases estradiol concentrations without affecting adrenal corticosteroids or aldosterone.	Advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy. Patients with ER- disease and patients who did not respond to tamoxifen rarely responded to letrozol.
Dose Range	**Side Effects**
2.5 mg PO QD.	AU: BLANK. ANY SIDE EFFECTS?

AU:ABBREVIATION CORRECT: ER-=estrogen receptor?

Megestrol (Megace, others) 23

Mechanism of Action	Indications
Progestational agent.	Pallitative therapy of breast cancer.
Dose Range	**Side Effects**
40 mg PO QD.	AU: BLANK. ANY SIDE EFFECTS?

Methotrexate (various) 24

Mechanism of Action	Indications
Antimetabolite; inhibits dihydrofolate reductase.	Adjuvant and metastatic breast cancer.
Dose Range	**Side Effects**
Various regimens (see common chemotherapy regimens sections).	Hematologic toxicity, oral mucosa toxicity (gingivitis, stomatatis), acute and chronic hepatotoxicity, pulmonary toxicity (including pneumonitis and pulmonary fibrosis), and occasional fatal cutaneous reactions (Stevens-Johnson syndrome). Use with care in patients with fluid collections (ie, ascites, effusions).

Paclitaxel (Taxol) for Node-Positive Breast Cancer 25

Mechanism of Action	Indications
Microtubule assembly stabilization.	Adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin containing therapy.
Dose Range	**Side Effects**
Manufacturer recommends: Dexamethasone 20 mg PO 12 hours and 6 hours prior, Diphenhydramine: 50 mg IV and either IV Cimetidine (300 mg) or Ranitidine (50 mg) 30–60 minutes before Paclitaxel. 175 mg/m2 IV over 3 hours every 3 weeks x 4 cycles.	Hematologic toxicity, infectious complications, eosinophilia, hypersensitivity reactions, peripheral neuropathy, hypotension and bradycardia, ECG abnormalities, arrhythmias, nausea and vomiting, alopecia, arthralgias and/or myalgias, and abnormalities in LFTs.

IV=intravenous
ECG=electrogcardiograph
LFTs=liver function tests

Paclitaxel (Taxol) for Advanced Breast Cancer 26

Mechanism of Action	Indications
AU: ANY MECHANISM?	Treatment of advanced breast cancer.
Dose Range	**Side Effects**
175 mg/m2 IV over 3 hours every 3 weeks x 4 cycles or 80–90 mg/m2 IV every week.	Hematologic toxicity, infectious complications, eosinophilia, hypersensitivity reactions, peripheral neuropathy, hypotension and bradycardia, ECG abnormalities, arrythmias, nausea and vomiting, alopecia, arthralgias and/or myalgias, and abnormalities in LFTs.

IV=intravenous
ECG=electrogcardiograph
LFTs=liver function tests

Tamoxifen (Nolvadex) for Adjuvant Breast Cancer 27

Mechanism of Action	Indications
Antiestrogen	Adjuvant breast cancer and to reduce the incidence of invasive breast cancer in women at high risk for developing breast cancer.
Dose Range	**Side Effects**
20 mg PO QD x 5 years.	AU: SIDE EFFECTS?

Tamoxifen (Nolvadex) Metastatic Breast Cancer 28

Mechanism of Action	Indications
Antiestrogen	Metastatic breast cancer
Dose Range	**Side Effects**
20 mg PO QD	AU: SIDE EFFECTS?

Thiotepa (Thioplex) 29

Mechanism of Action	Indications
Alkylating agent	Metastatic breast cancer
Dose Range	**Side Effects**
0.3–0.4 mg/kg IV every 1–4 weeks. Intrathecally: 1–10 mg/m2 once or twice weekly.	Hematologic toxicity and GI side effects are infrequent. Intrathecal administration associated with lower extremity weakness and pain and demyelination within the spinal cord in some patients. Transient parasthesias of the lower extremities has also been noted.

IV=intravenous
GI=gastrointestinal

Toremifene (Fareston) 30

Mechanism of Action	Indications
Nonsteroidal antiestrogen	Metastatic breast cancer
Dose Range	**Side Effects**
60 mg PO QD	AU: BLANK. ANY SIDE EFFECTS?

IV=intravenous
GI=gastrointestinal

Trastuzumab (Herceptin) 31

Mechanism of Action	Indications
Humanized monoclonal antibody directed at the HER-2 neu receptor	Adjuvant (in clinical trials) and metastatic breast cancer. Most responses seen in tumors that are 3+ by IHC or FISH.
Dose Range	**Side Effects**
Initial dose of 4 mg/kg IV over 90 minutes. Subsequent weekly doses consist of 2 mg/kg IV infused over 30 minutes.	Deaths associated with pulmonary reactions (including ARDS), infusion-related reactions, and hypersensitivity reactions. Severe cardiotoxicity has been reported and increases substantially with an anthracycline (this combination is not recommended). Diarrhea, nausea, and vomiting have also been reported.

IHC=; FISH=fluorescence in situ hybridization
IV=intravenous
AU: ARDS=??

Vinorelbine (Navelbine) 32

Mechanism of Action	Indications
Inhibits microtubule formation.	Advanced and metastatic breast cancer.
Dose Range	**Side Effects**
Monotherapy: 20–30 mg/m2 per week. **Combination chemotherapy:** various schedules.	Hematologic toxicity, asthenia, and fatigue, and peripheral neuropathy manifested by paresthesia and hypesthesia. Nausea and vomiting, constipation, and increase serum AST. Acute shortness of breath and bronchospasm have also been reported.

AU: AST=?

Diethylstilbestrol 33

Mechanism of Action	Dosage and Administration
Diethylstilbestrol is a synthetic estrogen used for breast cancer and prostate cancer treatment. Because of its dichotomous effects on breast cancer, tumor flare at physiological doses and regression at pharmacologic doses, the dosage for breast cancer should be in the pharmacologic range.	Breast cancer: 5 mg TID.
Toxicities	**Indications**
GI: Nausea and vomiting, cholestatic jaundice, and increased gallbladder disease. **Cardiovascular:** Exacerbation of congestive heart failure and thromboembolism. **GU:** Vaginal bleeding and candidiasis, cystitis-like symptoms. **Metabolic:** Hypercalcemia and fluid retention. **CNS:** Headache, migraine, and mental depression. **Skin:** Pigmentation of nipple and axillae **Breasts:** Gynecomastia in males. **Tumor flare:** 5%–10%.	FDA-approved for postmenopausal female patients or male patients with advanced breast cancer.
Contraindications	**Drug Interactions**
Pregnancy, active thrombophlebitis, known or suspected estrogen-dependent malignancy.	None directly. However, estrogen decreases the prothrombin time, impairs glucose tolerance, and increases the thyroid-binding globulin.
Response Rates	**Availability**
Approximately 30% of postmenopausal breast cancers and 55%–60% of ER+ cancers will respond. The response rate in males with breast cancer is similar to that in females.	Distributed by Eli Lilly and Co., Indianapolis IN in 0.1, 0.25, 0.5, 1, 2, 5, and 10 mg tablets and stored in light-protected container at room temperature.

GI=gastrointestinal ; GU=genitourinary
ER-=estrogen receptor ; CNS=central nervous syste
FDA=Food and Drug Administration

Fluoxymesterol (Halotestin) 34

Mechanism of Action	Dosage and Administration
Fluoxymesterol is a synthetic androgen used for the treatment of advanced breast cancer. The response rate is lower than that of tamoxifen. It can be used as fourth-line therapy. The erythropoietic effects may provide a sense of well-being in anemic patients.	10 mg BID orally
Toxicities	**Indications**
GU: Virilization, amenorrhea, and irregular menstrual periods. **GI:** Nausea, cholestatic jaundice. **Hematologic:** Suppression of clotting factors, and polycythemia. **CNS:** Increased libido, headache, anxiety, aggressiveness, and depression. **Skin:** Acne and hirsutism. Endocrine: Hypercalcemia.	FDA-approved for advanced breast cancer.
Contraindications	**Drug Interactions**
Known hypersensitivity to the drug, suspected prostate cancer, pregnancy, serious cardiac, hepatic, or renal disease.	Increases the sensitivity to anticoagulants, decreases the requirement for insulin and interferes with laboratory testing for thyroid function.
Response Rates	**Availability**
Breast cancer: 15%–25%.	Distributed by Upjohn Co., Kalamazoo, MI in 2, 5, and 10 mg tablets.

GU=genitourinary
GI=gastrointestinal
CNS=central nervous system
FDA=Food and Drug Administration

Goserelin Acetate (Zoladex) 35

Mechanism of Action	Dosage and Administration
Goserelin acetate is a synthetic decapeptide analogue of LHRH with a very prolonged half-life and 100 times greater potency than that of the natural releasing hormone. Therefore, it downregulates the LHRH receptors and reduces the release of gonadotropic hormones, which in turn results in a decrease in blood testosterone or estrogen levels. Thus, the functional result of LHRH analogue therapy is equivalent to surgical oophorectomy.	A depot dose of 3.6 mg/implant given subcutaneously every 4 weeks
Toxicities	**Indications**
Endocrine: Sexual dysfunction and tumor flare due to initial agonist properties **Respiratory:** Bronchitis. Cardiovascular: Hot flushes, arrhythmias, and hypertension. **CNS:** Depression, anxiety, and headache. **GI:** Constipation, diarrhea, and dyspepsia.	FDA-approved for premenopausal breast cancer.
Contraindications	**Drug Interactions**
Pregnant or nursing patients. History of hypersensitivity to LHRH.	None.
Response Rates	**Availability**
Pre- and perimenopausal receptor-positive advanced breast cancer: 45%.	Supplied by Zeneca Pharmaceutics, Wilmington, DE in a 3.6 mg disposable syringe device and stored at a room temperature of <25°C.

LHRH=lutenizing hormone-releasing hormone
CNS=central nervouse
GI=gastrointestinal
FDA=Food and Drug Administration

Leuprolide Acetate (Lupron dDpot) 36

Mechanism of Action	Dosage and Administration
Leuprolide acetate is a synthetic nonapeptide analogue of naturally LHRH. It desensitizes the LHRH receptor and reduces the production of gonadotropic hormones. It acts as medical castration in reducing estrogens in premenopausal women.	7.5 mg depot administered intramuscularly every month.
Toxicities	**Indications**
Endocrine: Sexual dysfunction and tumor flare due to initial agonist properties. Respiratory: Bronchitis. **Cardiovascular:** Hot flushes, arrhythmias, and hypertension. **CNS:** Depression, anxiety, and headache. **GI:** Constipation, diarrhea, and dyspepsia.	FDA-approved for palliative treatment of premenopausal advanced breast cancer.
Contraindications	**Drug Interactions**
History of hypersensitivity to the drug. Pregnant or nursing patients.	None reported.
Response Rates	**Availability**
40%–45% response rates have been observed in premenopausal patients with ER+ advanced breast cancer.	Supplied by TAP Pharmaceuticals, Deerfield, IL as 3.75, 7.5, and 22.5 mg depot formulations for IM injection. Store at room temperature and protect from freezing.

LHRH=lutenizing hormone-releasing hormone
CNS=central nervous system
GI=gastrointestinal
FDA=Food and Drug Administration
IM=intramuscular
ER=estrogen receptor.

Megestrol Acetate (Megace) 37

Mechanism of Action	Dosage and Administration
Megestrol acetate is a synthetic progestational drug used in the treatment of advanced breast cancer and endometrial cancer. At higher dosages, it is also used to improve anorexia and cachexia in cancer and AIDS patients. Progestins have significant antiestrogenic effect through either the conversion of estradiol to a less active estrone or downregulation of estrogen receptors.	Breast cancer: 40 mg tablet four times daily PO. Cachexia/anorexia: 400–800 mg of PO suspension daily in divided doses.
Toxicities	**Indications**
Metabolic: Weight gain, hypercalcemia, and fluid retention. **Cardiovascular:** Thromboembolic episodes, hypertension, and dyspnea. **GI:** Nausea and vomiting.	FDA-approved for advanced breast cancer and cancer-related cachexia.
Contraindications	**Drug Interactions**
Early stage of pregnancy.	Decreases the clearance of warfarin.
Response Rates	**Availability**
Approximately 60% of steroid receptor–positive breast cancer patients respond to megestrol. The newer aromatase inhibitors have an equivalent response rate to megestrol.	Supplied by Bristol-Myers-Squibb, Princeton, NJ as 20 and 40 mg tablets that are stored at room temperature. Also available in 40 mg micronized megestrol acetate per milliliter oral suspension to be stored at <25°C.

AIDS=acquired immunodeficiency virus
GI=gastrointestinal
FDA=Food and Drug Administration

Mifepristone (Mifiprex) 38

Mechanism of Action	Dosage and Administration
Mifepristone is a synthetic derivative of progesterone. It acts as an antiprogestin and antiglucocorticoid. It has antitumor effect on rat mammary tumors and human breast cancer and meningioma cell lines. Clinical trials in Europe have shown tumor regression with mifepristone in human breast cancers.	100–200 mg BID.
Toxicities	**Indications**
In general, mifepristone is well tolerated. **Major side effects:** Nausea, anorexia, hot flushes, dizziness, lethargy, and gynecomastia (in male patients).	FDA-approved for the medical termination of pregnancy through 49 days of pregnancy. It is not approved for the treatment of cancer.
Contraindications	**Drug Interactions**
Pregnant patients.	None reported.
Response Rates	**Availability**
Mifepristone showed minimal activity against breast cancer in two small European trials. Preliminary results from a recent Canadian phase II study also showed a modest antitumor activity, as partial responses were observed in 2 out of 22 patients.	Distributed by Danco Laboratories, New York, NY in 200 mg tablets.

FDA=Food and Drug Administration

Tamoxifen (Nolvadex) 39

Mechanism of Action	Dosage and Administration
Tamoxifen is a nonsteroidal SERM that exerts its effect on breast cancer by competitively inhibiting the binding of estrogen to estrogen receptors.	20 mg QD.

Toxicities	Indications
Vascular: Hot flashes, lightheadedness, and thromboembolism. **Gynecologic:** Vaginal bleeding, altered menses, ovarian cyst, and increased incidence of endometrial cancer. **GI:** Nausea, vomiting, and anorexia. Metabolic: Hypercalcemia. **CNS:** Emotional instability, depression, and transient ischemic attacks. **Ophthalmologic:** At prolonged high dosage some visual disturbance, such as macular retinopathy and corneal opacity, can occur.	FDA-approved for female and male advanced breast cancer; adjuvant therapy after surgical removal of primary breast cancer lesion; in combination with chemotherapy; breast cancer risk reduction in high-risk patients. Tamoxifen has been used for other forms of cancer, such as melanoma.

Contraindications	Drug Interactions
Known hypersensitivity to tamoxifen; pregnant patients; previous thromboembolic disease.	Tamoxifen is a cytostatic drug that blocks the cell cycle at the late G1 phase; therefore, it may attenuate cytotoxicity of many chemotherapeutic agents such as 5-FU and doxorubicin.

Response Rates	Availability
When tamoxifen is used as first-line hormonal therapy, ~60%–70% of steroid receptor–positive female and male advanced breast cancers respond.	Supplied by AstraZeneca Pharmaceutics, Wilmington, DE, in 10 and 20 mg tablets stored at room temperature and protected from heat and light.

SERM=selective estrogen receptor modulator
GI=gastrointestinal
CNS=central nervous system
FDA=Food and Drug Administration
5-FU=5-fluorouracil

Anastrozole (Arimidex) 40

Mechanism of Action	Dosage and Administration
Anastrozole is a nonsteroidal aromatase inhibitor for the treatment of postmenopausal breast cancer. It specifically suppresses the enzyme that converts androgens to estrogens, with no effect on corticosteroid or aldosterone synthesis.	1 mg QD orally.
Toxicities	**Indications**
The drug is generally well tolerated. **Main side effects:** GI disturbance, headache, hot flashes, and edema. Rashes and CNS symptoms (eg, lethargy) may occur but much less often than with first-generation aromatase inhibitors.	For advanced breast cancer in postmenopausal patients, especially those with ER+ tumors and a prior history of response to tamoxifen. May be used as first-line hormonal therapy for advanced breast cancer.
Contraindications	**Drug Interactions**
None known.	Although anastrozole inhibits reactions catalyzed by certain CYP 450 enzymes, it does not have known interactions with other drugs.
Response Rates	**Availability**
In patients previously treated with tamoxifen for advanced breast cancer, approximately one-third had either an objective response (10%) or stable disease (24%), with an overall median time to progression of 21 weeks. In previously untreated patients, response rates to anastrozole are similar to those of tamoxifen.	Distributed by Zeneca Pharmaceuticals, Wilmington, DE, in 1 mg tablets stored at room temperature between 20°–25° C.

GI=gastrointestinal
CNS=central nervous system
R=estrogen receptor
CYP 450=cytochrome P450

Letrozole (Femara) 41

Mechanism of Action	Dosage and Administration
Letrozole is a newer selective and potent aromatase inhibitor. The circulating estrogens decrease by more than 95% within 2 weeks of daily doses of letrozole, with no change in aldosterone or clinically significant changes in cortisol levels. It is used for the treatment of advanced breast cancer in postmenopausal patients with disease progression following antiestrogen therapy or as first-line therapy.	2.5 mg QD orally.
Toxicities	**Indications**
Letrozole is well tolerated. **Main side effects:** Transient thrombocytopenia and elevation of liver transaminases have been reported. **Minor side effects:** Fatigue, nausea, vomiting, musculoskeletal pain, headache, hypertension, dyspnea, hot flashes, and depression.	Used as a first-, second-, or third-line hormonal therapy for advanced breast cancer.
Contraindications	**Drug Interactions**
In pregnant woman or patients with known hypersensitivity to this drug.	**au: none?**
Response Rates	**Availability**
As first-line therapy, response rates and time to treatment progression are slightly superior to tamoxifen. Objective responses to letrozole as a second- and third-line hormonal therapy in patients with advanced breast cancer are ~24% and ~22%, respectively.	Distributed by Novartis, East Hanover, NJ in 2.5 mg tablets stored at room temperature.

Toremifene (Fareston) 42

Mechanism of Action	Dosage and Administration
Toremifene is a nonsteroidal antiestrogen used for the treatment of advanced breast cancer in patients with steroid-receptor–positive disease. It appears to be nearly identical to tamoxifen in action and side effects. However, it has fewer tumorigenic effects in a rodent hepatic model, although this may not be clinically relevant.	60 mg QD orally.
Toxicities	**Indications**
Most common side effects: Hot flashes, nausea, vaginal discharge or bleeding, and dizziness. **Minor side effects:** Anorexia, headache, diarrhea, vaginitis, rash, pruritus, depression, and insomnia. **Miscellanous side effects:** Thromboembolic events, elevated LFTs, and hypercalcemia.	FDA-approved for the treatment of advanced breast cancer in postmenopausal patients.
Contraindications	**Drug Interactions**
Should not be used in pregnant patients.	May interact with coumarin and CYP 450 inducers (phenobarbital, phenytoin) or inhibitors (ketoconazole).
Response Rates	**Availability**
As a first-line hormonal therapy for ER+ or unknown advanced breast cancer, the response rates (21%–31%) in various randomized trials are comparable to that of tamoxifen (19%–37%). Time to progression and overall survival are also comparable. Unlike the aromatase inhibitors, it does not appear to be useful in patients who have progressive disease on tamoxifen.	Distributed by Schering, Kenilworth, NJ as 60 mg tablets stored at room temperature and protected from heat and light.

LFTs=liver function tests
CYP 450=cytochrome P450
ER=estrogen receptor positive

Exemestane (Aromasin) 43

Mechanism of Action	Dosage and Administration
Exemestane is a steroidal aromatase inhibitor for the treatment of postmenopausal breast cancer. It specifically suppresses the enzyme that converts androgens to estrogens, with no effect on corticosteroid or aldosterone synthesis. Compared to anastrazole and letrozole, exemestane binds irreversibly to the aromatase substrate binding site. This causes downregulation of aromatase. It is unclear if this mechanism of action correlates with enhanced clinical response.	25 mg QD orally.
Toxicities	**Indications**
The drug is generally well tolerated. **Main side effects:** Hot flashes, nausea, fatigue, and increased sweating.	FDA-approved for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed on tamoxifen. For advanced breast cancer in postmenopausal patients, especially those with estrogen-receptor–positive tumors and a prior history of response to tamoxifen. Exemestane is also effective for patients who have progressed on anastrazole.
Contraindications	**Drug Interactions**
None known.	Although exemestane inhibits reactions catalyzed by certain P450 enzymes, it does not have known interactions with other drugs.
Response Rates	**Availability**
Early results suggest that first-line treatment of ER+ breast cancer results in an objective response rate at least equivalent, if not better, than tamoxifen. For patients who have progressed on tamoxifen therapy, the objective response rate is about 15% and stable disease is 22%. In this setting, median time to treatment failure is 16 weeks.	Distributed by Pharmacia, Peapack, NJ in 25 mg tablets stored at room temperature between 20°–25°C.

FDA=Food and Drug Administration
CYP 450=cytochrome 450
ER+=estrogen receptor positive

Fulvestrant (ICI 182, 780) 44

Mechanism of Action	Dosage and Administration
Fulvestrant (ICI 182,780) is a pure steroidal anti-estrogen currently in phase III clinical trials. Unlike other SERMs, fulvestrant is a pure anti-estrogen in all tissues studied. It also causes degradation of the estrogen receptor resulting in a decreased cellular concentration of the receptor. Early clinical trials suggest it is useful in patients who have progessive disease on tamoxifen.	250 mg monthly injection.
Toxicities	**Indications**
The side effect profile of fulvestrant is not completely known. However, there appears to be no induction of hot flashes, endometrial stimulation, or vaginal dryness.	au: ??
Contraindications	**Drug Interactions**
au ??	au ??
Response Rates	**Availability**
Early results suggest that good responses can be obtained in patients who have progressed through tamoxifen suggesting a lack of cross resistance.	Fulvestrant is currently undergoing phase III clinical trial in the US. It will be distributed as Faslodex by AstraZeneca, Wilmington, DE.

FDA=Food and Drug Administration
CYP 450=cytochrome 450
ER+=estrogen receptor positive

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