with short disease-free intervals, rapidly progressive visceral disease, lymphangitic pulmonary disease, or intracranial disease are unlikely to respond to endocrine therapy.

In many cases, systemic therapy can be withheld while the patient is managed with appropriate local therapy. Radiation therapy and occasionally surgery are effective at relieving the symptoms of metastatic disease, particularly when bony sites are involved. Many patients with bone-only or bone-dominant disease have a relatively indolent course. Under such circumstances, systemic chemotherapy has a modest effect, whereas radiation therapy may be effective for long periods. Other systemic treatments, such as strontium-89 and/or bisphosphonates, may provide a palliative benefit without inducing objective responses. Most patients with metastatic disease, and certainly all who have bone involvement, should receive concurrent bisphosphonates. Because the goal of therapy is to maintain well-being for as long as possible, emphasis should be placed on avoiding the most hazardous complications of metastatic disease, including pathologic fracture of the axial skeleton and spinal cord compression. New back pain in patients with cancer should be explored aggressively on an emergent basis; to wait for neurologic symptoms is a potentially catastrophic error. Metastatic involvement of endocrine organs can cause profound dysfunction, including adrenal insufficiency and hypopituitarism. Similarly, obstruction of the biliary tree or other impaired organ function may be better managed with a local therapy than with a systemic approach.

Many patients are inappropriately treated with toxic regimens into their last days of life. Often oncologists are unwilling to have the difficult conversations that are required with patients nearing the end of life, and not uncommonly, patients and families can pressure physicians into treatments with very little survival value. Palliative care consultation and realistic assessment of treatment expectations need to be reviewed with patients and families. We urge consideration of palliative care consultations for patients who have received at least two lines of therapy for metastatic disease.

Endocrine Therapy Normal breast tissue is estrogen dependent. Both primary and metastatic breast cancer may retain this phenotype. The best means of ascertaining whether a breast cancer is hormone dependent is through analysis of estrogen and progesterone receptor levels on the tumor. Tumors that are positive for the estrogen receptor and negative for the progesterone receptor have a response rate of ~30%. Tumors that are positive for both receptors have a response rate approaching 70%. If neither receptor is present, the objective response rates are <5%. Receptor analyses provide information as to the correct ordering of endocrine therapies as opposed to chemotherapy. Because of their lack of toxicity and because some patients whose receptor analyses are reported as negative respond to endocrine therapy, an endocrine treatment should be attempted in virtually every patient with metastatic breast cancer. Potential endocrine therapies are summarized in **Table 108-4**. The choice of endocrine therapy is usually determined by toxicity profile and availability. In most postmenopausal patients, the initial endocrine therapy should be an aromatase inhibitor rather than tamoxifen. For the subset of postmenopausal women who are estrogen receptor–positive but also HER2/neu-positive, response rates to aromatase inhibitors are substantially higher than to tamoxifen. Aromatase inhibitors are not used in premenopausal women because their hypothalamus can respond to estrogen deprivation by producing gonadotropins that promote estrogen synthesis. Newer "pure" antiestrogens that are free of agonistic effects are also effective. Cases in which tumors shrink in response to tamoxifen withdrawal (as well as withdrawal of pharmacologic doses of estrogens) have been reported. A series of studies with aromatase inhibitors, tamoxifen, and fulvestrant have all shown that the addition of everolimus to the hormonal treatment can lead to significant benefit after progression on the endocrine agent alone. Everolimus (an mTOR inhibitor) in coordination with endocrine agents is now being explored as front-line therapy and in the adjuvant setting. Endogenous estrogen formation may be blocked by analogues of luteinizing hormone–releasing hormone in premenopausal women. Additive endocrine therapies, including treatment with progestogens, estrogens, and androgens, may also be tried in patients who respond to initial endocrine therapy; the mechanism of action of these latter therapies is unknown. Patients who respond to one endocrine therapy have at least a 50% chance of responding to a second endocrine therapy. It is not uncommon for patients to respond to two or three sequential endocrine therapies; however, combination endocrine therapies do not appear to be superior to individual agents, and combinations of chemotherapy with endocrine therapy are not useful. The median survival of patients with metastatic disease is approximately 2 years, although many patients, particularly older persons and those with hormone-dependent disease, may respond to endocrine therapy for 3–5 years or longer.

TABLE 108-4 ENDOCRINE THERAPIES FOR BREAST CANCER

Therapy	Comments
Castration	For premenopausal women
Surgical	
LHRH agonists	
Antiestrogens	
Tamoxifen	Useful in pre- and postmenopausal women[a]
"Pure" antiestrogens	Responses in tamoxifen-resistant and aromatase inhibitor–resistant patients[a]
Surgical adrenalectomy	Rarely used second-line choice
Aromatase inhibitors	Low toxicity; now first choice for metastatic disease[a]
High-dose progestogens	Common fourth-line choice after aromatase inhibitors, tamoxifen, and fulvestrant
Hypophysectomy	Rarely used
Additive androgens or estrogens	Plausible fourth-line therapies; potentially toxic

[a]Consider retreatment with Everolimus in combination for disease progression

Abbreviation: LHRH, luteinizing hormone–releasing hormone.

Chemotherapy Unlike many other epithelial malignancies, breast cancer responds to multiple chemotherapeutic agents, including anthracyclines, alkylating agents, taxanes, and antimetabolites. Multiple combinations of these agents have been found to improve response rates somewhat, but they have had little effect on duration of response or survival. The choice among multidrug combinations frequently depends on whether adjuvant chemotherapy was administered and, if so, what type. Although patients treated with adjuvant regimens such as cyclophosphamide, methotrexate, and fluorouracil (CMF regimens) may subsequently respond to the same combination in the metastatic disease setting, most oncologists use drugs to which the patients have not been previously exposed. Once patients have progressed after combination drug therapy, it is most common to treat them with single agents. Given the significant toxicity of most drugs, the use of a single effective agent will minimize toxicity by sparing the patient exposure to drugs that would be of little value. No method to select the drugs most efficacious for a given patient has been demonstrated to be useful.

Most oncologists use either an anthracycline or paclitaxel following failure with the initial regimen. However, the choice has to be balanced with individual needs. One randomized study has suggested that docetaxel may be superior to paclitaxel. A nanoparticle formulation of paclitaxel (Abraxane) is also effective.

The use of a humanized antibody to *erbB2* (trastuzumab [Herceptin]) combined with paclitaxel can improve response rate and survival for women whose metastatic tumors overexpress *erbB2*. A novel antibody conjugate (ADC) that links trastuzumab to a cytotoxic agent has been approved for management of HER2-positive breast cancer. The magnitude of the survival extension is modest in patients with metastatic disease. Similarly, the use of bevacizumab