Hormonal Modulation in the Treatment of Breast Cancer

Kerin Adelson, MD[a,*], Doris Germain, PhD[b], George Raptis, MD, MBA[a], Noa Biran, MD[c]

KEYWORDS

• Hormonal modulation • Breast cancer • Aromatase inhibitors • Ovarian suppression • GnRH agonist • Antiestrogens • SERM • SERD

BREAST CANCER EPIDEMIOLOGY

Breast cancer is the most commonly diagnosed malignancy in women worldwide. It is estimated that 207,090 women were diagnosed with and 39,840 women died of breast cancer in 2010. Surveillance, Epidemiology and End Results data predict that 12% of women born today, or 1 in 8 women, will be diagnosed with breast cancer in their lifetime. Long-term survival rates are closely linked to breast cancer stage at presentation. Sixty percent of women are diagnosed when the cancer is confined to the breast (without lymph node involvement), and these women have an excellent 5-year relative survival of 98%. Thirty-three percent of women with breast cancer present with disease that has spread to local/regional lymph nodes and for this group, 5-year relative survival is 83.6 %. Only 5% of women with breast cancer present with initial metastatic disease, and for this population 5-year relative survival is only 23.4% and close to none are cured of the cancer.[1]

Breast cancer can metastasize many years after the initial diagnosis and treatment. Thus, the 5-year relative survival statistics omit recurrences that occur after 5 years, which is more common in women treated with adjuvant chemotherapy, trastuzumab, or hormonal modulation than in most other cancers. Furthermore, most of these relapses are outside the breast, leading to incurable stage IV disease. Despite recent advances in breast cancer therapy and earlier diagnosis with screening, 24% to 30%

Disclosures: Dr Adelson has worked as a consultant for GTx pharmaceuticals.
[a] Division of Hematology and Medical Oncology, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1079, New York, NY 10029, USA
[b] Division of Hematology/Oncology, Department of Medicine, Tisch Cancer Insitute, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1079, New York, NY 10029, USA
[c] Samuel Bronfman Department of Medicine, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029, USA
* Corresponding author.
E-mail address: kerin.adelson@mssm.edu

Endocrinol Metab Clin N Am 40 (2011) 519–532
doi:10.1016/j.ecl.2011.05.011 **endo.theclinics.com**
0889-8529/11/$ – see front matter

of women with node-negative disease at diagnosis will eventually experience a disease recurrence, and 40% to 80% of women with node-positive disease will experience relapse. When distant metastases occur, the prognosis is poor, with a median survival of 18 to 36 months from time of recurrence.[2] Thus, an urgent need still exists to improve curative treatments for women with breast cancer and to improve efficacy of treatment for women with metastatic disease.

Metastatic relapse is generally explained by the theory that many women with primary breast cancer have subclinical metastases at presentation.[3] Surgery and radiotherapy are targeted at removing the primary tumor and preventing local relapse, while systemic treatments including chemotherapy, hormonal modulation, and Her-2 targeted immunotherapy, are directed at eliminating micrometastases. Systemic treatments given before surgery are called neoadjuvant therapy and those given after surgery are called adjuvant therapy.

In the United States and Canada, breast cancer incidence has recently leveled off and even decreased slightly in age groups older than 45 years.[4] One theory attributed the decline in incidence to the reduced use of hormone replacement therapy (HRT) after the Women's Health Initiative study showed HRT increased incidence of breast cancer and failure to prevent cardiac and thrombotic events.[5]

ESTROGEN RECEPTOR EXPRESSION AND HORMONAL MODULATION IN BREAST CANCER

Seventy percent of breast cancers express the estrogen receptor (ER) and usually have a lower-grade phenotype than ER-negative cancers. During the first several years after diagnosis, patients with ER-positive tumors tend to have a lower recurrence rate than those with ER-negative tumors. The recurrence rate of ER-positive tumors remains stable through years 6 or 7 and drops thereafter. Most importantly, ER status is an important predictor of the likelihood of response to endocrine therapies. In patients with localized disease, adjuvant hormonal modulation is used for 5 to 10 years to reduce the risk of distant recurrence. When metastases occur in women receiving an adjuvant therapy, tumors are likely to have primary or acquired resistance to that agent.

Although many laboratories have described mechanisms of resistance to endocrine therapies, none of these mechanisms have been clinically validated to guide treatment decisions. Thus, the choice of an adjuvant hormonal agent depends entirely on the patient's menopausal status; women with intact ovarian function receive selective estrogen receptor modulators (SERMs) and postmenopausal women receive aromatase inhibitors (AIs).

Women with metastatic breast cancer require treatment for the duration of their lives. In this setting, hormonal therapy is used to slow tumor progression. Hormonal modulation is highly effective and less toxic than chemotherapy. However, in this population a significant portion of ER-positive tumors will not respond to antiestrogen therapy initially, and most that do respond will ultimately develop resistance. Once the tumor becomes resistant to therapies to which it has been exposed, cytotoxic chemotherapy is required. Both primary and acquired resistance to endocrine therapy underscore the need to develop new treatments and to better tailor which treatments are chosen for which tumors.

This article explores the history of endocrine therapy for the treatment of breast cancer, the clinical evidence behind the current standards of care and controversies that may change these standards in the future.