22 Metastatic Breast Cancer: Tailored Endocrine Therapy for Premenopausal Women

TATIANA M. PROWELL AND NANCY E. DAVIDSON

22.1 Introduction

One-quarter of breast cancer patients are premenopausal at the time of diagnosis [1], and 60% are steroid hormone-receptor-positive (HR+) [2]. Fortunately, only 5% of patients present with disseminated disease, but more than 20% will ultimately become metastatic [3]. Steroid hormone-receptor expression strongly predicts efficacy of endocrine manipulation, producing responses in approximately 60% of women with estrogen receptor (ER)- and progesterone receptor (PR)-positive (ER+/PR+) breast cancer, 30% with either ER+ or PR+ alone, and fewer than 10% with ER-negative (ER−)/PR-negative (PR−) tumors [4, 5]. In addition, higher levels of ER and/or PR correlate with a greater likelihood of response to hormonal therapies [4]. Endocrine therapy is generally the first-line approach to HR+ metastatic disease, except in women with visceral or central nervous system involvement or rapidly progressing disease, because of its efficacy and favorable toxicity profile.

Options for endocrine therapy in premenopausal women with metastatic breast cancer include ovarian ablation via oophorectomy or ovarian irradiation, ovarian suppression via administration of luteinizing hormone-releasing hormone (LHRH) analogs, monotherapy with the selective ER modulator (SERM) tamoxifen, or the combination of these modalities. In addition, aromatase inhibitors, which inhibit peripheral conversion of androgens to estrogens, may be used in conjunction with ovarian ablation or suppression. Finally, progestins such as megestrol acetate are available for third-line endocrine therapy. The challenge is to determine for an individual patient whether these therapies are best combined or given as sequential monotherapy, and if given as monotherapy, the best order in which to give them.

22.2 Ovarian Ablation for Treatment of Metastatic Breast Cancer

22.2.1 Background

The majority of estrogen synthesis in premenopausal women takes place in the ovaries. Reduction of circulating estrogens to postmenopausal levels via oophorectomy was the original systemic treatment for breast cancer, first proposed more than a century ago. Response rates for ovarian ablation in premenopausal women with metastatic breast cancer have been reported to range from 14 to 70% [6]. While
oophorectomy or ovarian irradiation have been used historically to lower estrogens to postmenopausal levels, in the last decade, LHRH analogs, which act on the hypothalamic-pituitary-ovarian axis to suppress estrogen production, have assumed a central role in the management of premenopausal women with HR+ breast cancer of all stages.

22.2.2 Methods of Ovarian Ablation

22.2.2.1 Oophorectomy

Surgical castration was first proposed as a treatment for metastatic breast cancer in 1896 when a Scottish surgeon, George Beatson, observed a clinical response and long-term survival after removing the ovaries of a young lactating woman with advanced breast cancer [7]. Although oophorectomy rapidly reduces estrogen to postmenopausal levels in virtually 100% of premenopausal patients, it poses a small risk of surgical and anesthesia-related morbidity and mortality.

22.2.2.2 Ovarian Irradiation

Ovarian irradiation was first suggested for use in the treatment of breast cancer by Schinzinger in 1889, although it was not routinely applied for this purpose until the mid-20th century [8, 9]. Trials of ovarian irradiation have used a variety of doses and treatment schedules, from a single 450 cGy fraction up to a total of 2,000 cGy in 5–6 fractions [10, 11]. Ovarian irradiation is a relatively simple outpatient procedure, but its efficacy varies by schedule and patient age, and standard techniques for targeting the ovaries do not consistently result in ovarian failure. More than 10% of all women, and more than a third of women under age 35 years, fail to become amenorrheic following ovarian irradiation [12, 13]. In addition, estrogen levels take much longer to reach postmenopausal levels with ovarian irradiation compared to oophorectomy [14].

22.2.2.3 Ovarian Suppression with LHRH Agonists

Production of estrogen is controlled by the hypothalamic-pituitary-ovarian axis. The hypothalamus produces a pulsatile release of LHRH, which in turn stimulates pituitary release of the gonadotropins that control ovarian estrogen production (Fig. 22.1). LHRH analogs bind pituitary gonadotropin-releasing hormone (GnRH) receptors with greater affinity than endogenous LHRH, causing internalization of pituitary GnRH receptors and rendering the gonadotropic cells refractory to endogenous LHRH (Fig. 22.1). LHRH analogs therefore cause an initial rise in circulating estrogen levels, which are responsible for the well-described “tumor flare” phenomenon [15], followed by a fall to castrate levels within about 3 weeks [16]. While ovarian suppression avoids the morbidity associated with surgery or radiation and