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Management of breast cancer in very young women

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A B S T R A C T

Breast cancer is the leading cause of cancer-related deaths in women age 40 and younger in developed countries, and although generally improving, survival rates for young women with breast cancer remain lower than for older women. Young women are more likely to develop more aggressive subtypes of breast cancer and previous research has suggested that young age is an independent risk factor for disease recurrence and death, and there may be unique biologic features of breast cancer that occurs in young women. Certainly, there are host differences biologically as well as psychosocially that affect the management of breast cancer and survivorship concerns for young women compared to older women. Multi-agent chemotherapy and biologic therapy targeting the tumor similar to the treatment in older women is standard, with careful attention to unique survivorship concerns including genetics, infertility, and psychosocial issues. Select young women will do well with hormone therapy only, although at present, the optimal hormonal therapy for very young women remains unclear. Recent data demonstrating that 10 years of tamoxifen improves outcomes compared to 5 may be particularly beneficial for young women with hormone receptor-positive tumors given the risk benefit profile. Future and ongoing studies focused on breast cancer in young women, addressing both biology as well as psychosocial issues, including supportive care interventions should improve outcomes for young women with breast cancer.

Introduction

Breast cancer in young women is a relatively rare disease, however, an estimated 14,000 women under age 40 are diagnosed with breast cancer annually and nearly 3000 young women die each year from their disease, in the U.S. alone [1]. Thousands more are diagnosed worldwide, and the lowest five-year survival rates for breast cancer occur in young women both in western as well as in developing countries [2,3]. Breast cancer is the leading cause of cancer death in young women [1]. Furthermore, recent reports suggest that rates of distant disease at diagnosis are increasing for women aged 25–39 [4].

The reasons for worse outcomes in younger women are complex and are likely related to multiple factors, including unfavorable disease biology [5–10] and delays in diagnosis [11] due in part to both a lack of reliable screening and suboptimal access to care in this population [12]. In addition, age itself may independently contribute to outcomes, although the effect of age seems to vary within tumor subtypes for both systemic and local recurrence risk [13–16]. Young women also have increased risk of psychosocial distress after diagnosis of breast cancer, due in part not only to their more risky disease on average and associated aggressive therapy, but also to their stage of life at diagnosis. Young women are more likely to be concerned about fertility and family planning, sexual functioning, beauty and body image, launching/sustaining careers or education, or raising young children. All of these areas can be disrupted by a breast cancer diagnosis and treatment. In this review, we will focus on management issues facing young women with breast cancer, considering their disease and psychosocial concerns.

Disease biology

Young women with breast cancer are more likely than older women to develop more aggressive tumors, including higher rates of poorly differentiated cancers and lower rates of estrogen receptor (ER)-positivity [5,7]. Young women have also been definitively demonstrated from population-based data to be more likely to develop Human Epidermal Growth Factor Receptor 2 [HER2]-positive disease [10,17]. The reasons for the biologic differences in breast cancer by age are poorly understood. Although mutations in BRCA1 may explain some of the triple negative, high grade cancers observed in young women, the majority of cancers are not related

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to a clear genetic syndrome. In an analysis that compared Recurrence Score profiles among hormone receptor-positive cancers in women aged ≤ 40 with older patients (≥age 70), younger women had higher mean Recurrence Scores, a higher proportion of high recurrence scores, lower mean ER expression, and higher proliferation [18]. Whether there are features that are truly unique to characterize the biology of breast cancer in young women is unknown at this time however, and further research is clearly warranted [9,19,20].

A number of studies have shown that differences in biologic subtype of breast cancer may vary by race as a function of age. African-American women have increased risk of breast cancer at younger ages and are more likely to have higher grade, estrogen receptor-negative cancers even when compared to younger white women [12,17]. In the Carolina Breast Cancer Study, 39% of premenopausal African American women had basal-like breast cancers, while 36% had luminal A cancers. These rates were reported in comparison to the 16% of non-African American women who had basal-like cancers and the 54% who had luminal A disease [21].

Local therapy considerations

Despite a well-documented increased risk of local recurrence, young age alone is not a contraindication to breast conserving therapy given the equivalent survival seen in this population with either mastectomy or breast conservation [22,23]. Genetic issues regarding risk of new primary disease may play a role in decision-making about local therapy and therefore early genetic testing is prudent. For young women who opt for breast preservation, attention to margin status may be particularly important. In one evaluation including 37 women younger than 35 with lymph node-negative breast cancer having breast-conserving therapy, local recurrence rates were 50.0% for women with positive margins compared with 20.8% for those with negative margins [24]. In a more recent publication, women age 40 or younger with invasive disease had 10-year local recurrence-free survival of 84.4% with negative margins versus 34.6% with positive margins, whereas women over 40 years had local recurrence-free survival of 94.7% if margins were negative compared with 92.6% if margins were positive [25]. There is also increasing evidence that young women may benefit additionally from post-mastectomy breast irradiation in the setting of 1–3 positive axillary lymph nodes [26]. Yet, despite their increased risk and the clear benefits of adjuvant radiation therapy, population-based data published recently from the U.S. demonstrated that very young women are less likely to receive adjuvant breast irradiation after breast conserving surgery [27]. Further research is needed to understand and intervene to improve these trends.

Adjuvant chemotherapy

Few clinical trials have focused on treatment for the youngest patients, and thus data are usually limited in this regard. However, large trials including women across age groups have demonstrated consistent benefit with adjuvant chemotherapy with regard to recurrence and survival, particularly among the youngest women. In the Early Breast Cancer Trialists' Collaborative Group meta-analysis, adjuvant chemotherapy in women under age 50 reduced the annual breast cancer death rate by approximately 38%, an effect that was irrespective of hormone receptor status, tamoxifen use, node involvement, and other tumor characteristics [28]. These benefits were further enhanced after restriction to women with node-positive and/or ER-negative cancers [28]. In a large meta-analysis examining the additional benefits of taxane therapy for women with breast cancer, reductions in recurrence and survival were also apparent for women with higher risk cancers, independent of tumor characteristics or age [29].Evidence also suggests that women with Human Epidermal Growth Factor Receptor 2 (HER2)-positive breast cancers have similar outcomes when controlling for other known prognostic factors, and derive equivalent benefit from adjuvant trastuzumab as their older counterparts, as described in a recent analysis of age and outcomes among women treated on the HERA trial [15]. Further research is warranted in this area.

It is also important to recognize when considering adjuvant chemotherapy for risk reduction for a young women, that a 38% risk reduction [28] may represent a small absolute risk reduction and may, in part, be due to a chemoendocrine effect in premenopausal women with hormone-sensitive disease. Before committing a woman to chemotherapy simply because of her age, these absolute benefits must be thoughtfully weighed against the potential long term sequelae of chemotherapy. In the quantitative gene expression analysis by age reported by Shak et al., a wide range of Recurrence Scores was demonstrated for younger and older women, suggesting a continuum of biology that is not predicted by age alone [18]. However, it must be noted that outcomes data for the use of genomic predictors in the very young are limited to date [30].

Regardless of age, incorporation of the estimated risk of recurrence with regard to hormone receptor status, HER2 status, stage of disease, tumor grade, genomic risk profile when appropriate, competing risks, and patient preferences should guide decision-making in all patients, both younger and older patients. Consideration of host issues for young women may be particularly important given their concerns regarding fertility and alternative strategies either to avoid chemotherapy or to preserve fertility may be optimal for some young women [30,31].

Adjuvant hormonal therapy

Despite our understanding of the significant risk reduction provided by hormonal therapy in premenopausal women with hormone receptor-positive breast cancer, the optimal modality and duration of therapy has not been elucidated [30]. The standard hormonal therapy for premenopausal women with hormone receptor-positive breast cancer is tamoxifen, and recent data from the ATLAS trial has demonstrated that 10 years is more beneficial than 5 years. Given the low risk of serious toxicity in younger women (i.e., endometrial cancer and venous thrombosis), the risk-benefit ratio for extended tamoxifen therapy is particularly favorable for young women to receive up to 10 years of tamoxifen [33,34].

The benefits of ovarian suppression/ablation with and without tamoxifen are comparable to chemotherapy, and amenorrhea itself may be protective [35,36]. To date it is not clear that ovarian suppression adds to tamoxifen. The Suppression of Ovarian Function Trial (SOFT) (tamoxifen vs. triptorelin for ovarian suppression with tamoxifen vs. triptorelin with exemestane) will not only inform our hormonal therapy recommendations, but will also address important toxicity questions in young women. Recent data from the ABCSG-12 trial have demonstrated reassuring results with regard to the notion of replacing chemotherapy with hormonal therapy in selected patients [37]. Gnant and colleagues examined the effect of adding zolendronic acid to hormonal therapy with assignment to either (a) tamoxifen and goserelin or (b) anastrozole and goserelin in a 2 × 2 factorial design. Women on this study were premenopausal, had early stage breast cancer, and most did not receive adjuvant chemotherapy. Although the hormonal therapy groups did not differ with regard to outcomes, those who received zolendronic acid had a 3.2% absolute reduction in the risk of disease