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BREAST CANCER (B OVERMOYER, SECTION EDITOR)

Unique Aspects of Caring for Young Breast Cancer Patients

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Abstract Breast cancer is the most commonly diagnosed malignancy in young women in the USA. Although breast cancer mortality has decreased overall, survival rates in young women remain lower than those in older women. Young women with breast cancer comprise a special population due to the aggressive biology of their tumors as well as their unique psychosocial concerns. Although general treatment principles are similar regardless of age, recent developments from research focused on younger women have provided new insights to guide treatment of this special population. This article will focus on these new developments in areas including endocrine therapy and fertility preservation as well as the unique treatment-related sequelae and psychosocial concerns among young women with breast cancer face.

Keywords Young women · Breast cancer · Premenopausal · Age

Introduction

Breast cancer is the most commonly diagnosed malignancy and the second leading cause of cancer deaths among women in the USA. In 2014, it is estimated that more than 232,000 new breast cancers will be diagnosed [1]. Approximately 7 % of these new diagnoses will occur in women under the age of 40 [2]. While overall breast cancer mortality has declined over the past quarter century, likely due to improved detection and treatment, these encouraging trends have not been as evident in younger women [3, 4]. Few clinical trials have focused on the young, and some advances in care of postmenopausal women do not benefit the premenopausal population. Breast cancer in younger women tends to be diagnosed at a later stage, be of higher grade, has less estrogen receptor (ER) positivity, and has a greater chance of recurrence [5–10]. In fact, although somewhat controversial, there have been several studies that have suggested that young age is an independent prognostic factor for poor outcome [4–6, 11].

Young women with breast cancer comprise a unique population due to the biology of their tumors and their special psychosocial concerns. They are at higher risk of carrying a risk allele for hereditary breast cancer, experiencing treatment-related infertility, and suffering various other long-term physical and mental side effects of oncologic treatment. Over the past year, research focusing on young breast cancer patients has provided important new insights that inform the care of this generally understudied population. In this article, we will review the unique aspects of caring for young breast cancer patients with a focus on new data and developments.

Diagnosis

Historically, it has been assumed that poor prognoses in young breast cancer patients are at least in part due to substantial delays in diagnosis related to both lack of effective screening and low suspicion for breast cancer when a breast abnormality develops in the young. However, recent results from a prospective, multicenter cohort study of 585 women diagnosed with breast cancer at age ≤40 years revealed that 80 % of young women detect their own breast cancers and most do not experience long delays before diagnosis. Among women with self-detected cancers, only 17 % reported that they

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waited at least 90 days before they sought medical attention for a breast abnormality and only 12 % reported that there was at least a 90-day delay between the time they sought medical attention and when they were diagnosed with breast cancer. Women with fewer financial resources were found to be most likely to delay seeking medical attention for a self-detected breast abnormality. Neither of these types of delay was statistically significantly associated with higher stage at diagnosis [12]. These findings suggest that delays in diagnosis are not the primary driver behind poorer prognosis in young women. It is therefore unlikely that large improvements in outcomes will be achieved by eliminating delays in diagnosis of self-detected breast abnormalities (i.e., by encouraging young women and their providers to biopsy more quickly). It may be more impactful to focus on enhancing treatment efficacy for this population.

Local Therapy

Surgery

The general principles behind the surgical treatment of young women with breast cancer do not differ greatly from those for older women, but effects on body image and sexual health may be more in the forefront during the decision-making process for many young patients. For early-stage breast cancer, breast-conserving surgery (lumpectomy) followed by radiation therapy has been shown to have equivalent survival to modified radical mastectomy [13–15]. Young women have a higher risk of local recurrence, although this has not been shown to negatively impact survival after lumpectomy [16–19]. Therefore, current consensus guidelines for the treatment of young women with breast cancer recommend breast conservation when feasible [20•].

The Society of Surgical Oncology only recommends bilateral mastectomies in the setting of genetically predisposing mutations including BRCA or strong family history without identifiable mutation, in cases where surveillance of the contralateral breast would prove too difficult, or for esthetics and symmetry in patients who require unilateral mastectomy for the index lesion [21]. However, many young women choose bilateral mastectomy even when lumpectomy is recommended and the rates of contralateral prophylactic mastectomy among young women have been rising in recent years [22, 23]. In women ≤45 years old in the National Cancer Database with stage I–II breast cancer, contralateral prophylactic mastectomy rates increased from 9.3 % in 2003 to 26.4 % in 2010. In multivariate analysis, women ≤45 years old who underwent contralateral prophylactic mastectomy were more likely to be Caucasian and treated at an academic center [24]. A recent study assessing factors associated with surgical decisions showed that young women with stage I–III breast cancer under the age of 40 with high levels of anxiety are twice more likely to undergo mastectomy than breast-conserving surgery. Although 87 % of the 428 patients had stage I or II disease and only 14 % had a BRCA 1 or 2 mutation, 41 % underwent contralateral prophylactic mastectomy, 29 % had unilateral mastectomy, and 31 % had breast-conserving surgery. Other factors associated with contralateral prophylactic mastectomy were the presence of predisposing mutations, being a mother, and the patient being the main decision maker about surgery as opposed to shared decision-making between the patient and physician [25]. Most women who undergo contralateral prophylactic mastectomy report knowing that more aggressive surgery will not improve their survival but also paradoxically report that they undergo the procedure both to decrease their risk of contralateral breast cancer, which they often overestimate, and to improve their survival [25]. Communication between physicians and their patients to quell fears and to optimally explain surgical options is very important when treating young women with breast cancer.

Radiation Therapy

Given the higher risk of local recurrence in young women, radiation plays a particularly important role for this group. While some older women may be able to safely forego radiation after lumpectomy for small hormone receptor-positive cancers, this does not appear true in younger patients [26, 27]. In fact, in the EORTC 22,881–10,882 "boost versus no boost" trial, young women who received a 16 Gy boost to the tumor bed in addition to standard whole-breast radiation following lumpectomy with clear margins had a reduction in the 5-year local recurrence rate of 10 % [28, 29]. Nevertheless, some young patients do not receive the radiation they need and a recent large claims database study suggests that this may be partly due to the difficulty of finding adequate childcare to allow for weeks of daily therapy [30]. Acute toxicities of breast radiation do not appear worse in younger women, but data regarding the benefits of radiation treatment must be viewed in the context of potential long-term radiation side effects (e.g., cardiac damage) in the very young [31, 32].

Systemic Therapy

Chemotherapy

Younger patients frequently receive and benefit from systemic chemotherapy. The benefit/risk ratio for chemotherapy is superior when a tumor is more biologically aggressive and higher stage and when a patient is healthier (as young women usually are) at the time of diagnosis. Because younger women are more likely to have triple negative tumors than older

women, it is important to note that in the results from CALGB/Alliance, 40603 may be particularly relevant for this population [33]. This study showed that the addition of carboplatin to the taxane component of neoadjuvant paclitaxel followed by doxorubicin-cyclophosphamide increased the pathologic complete response rate from 46 to 60 % in patients receiving neoadjuvant therapy for early-stage cancers that were Her2 negative and <10 % in those that were positive for estrogen and progesterone receptor. While it is uncertain whether this will translate into a disease-free and overall survival benefit, it is encouraging that at least carboplatin may help more young women with triple negative cancers pursue breast-conserving therapy.

Endocrine Therapy

Until recently, 5 years of tamoxifen was the treatment of choice for young premenopausal women with estrogen receptor-positive (ER+) breast cancer. This recommendation was based on meta-analyses from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), which showed that 5 years of tamoxifen compared to no endocrine therapy was associated with an absolute risk reduction in breast cancer recurrence of 13 % at 15 years (33 vs. 46 %; relative risk (RR)=0.61). Tamoxifen was also associated with an absolute risk reduction of 9 % for breast cancer death at 15 years of follow-up (24 vs. 33 %; RR=0.70). This benefit was proven in various age groups including women less than 45 years old [34]. However, the recently released data from the ATLAS and aTTom trials suggest that taking tamoxifen for 10 years instead of 5 years provides further protection against breast cancer recurrence, with the greatest relative risk reduction in the 10–14-year time period [35••, 36]. The pooled analysis of the 17,477 women enrolled in either the ATLAS or aTTom trials showed an overall relative risk reduction of death of 9 % for patients receiving 10 years of tamoxifen instead of 5 years (RR=0.91; P=0.008). After 10 years of follow-up, the relative risk reduction increased to 16 % (RR=0.84; P=0.008) [35••, 36]. These data are especially relevant for premenopausal women because postmenopausal women have had the option to switch to an aromatase inhibitor at 5 years, but until now, there were no data to support the efficacy of extended endocrine therapy in the premenopausal population.

Importantly, toxicity data are encouraging with regard to the safety and tolerability of a longer tamoxifen course. In the ATLAS trial, the absolute 10-year risk of endometrial cancer in the mixed-age participants was increased from 1.6 to 3.1 % and the mortality from endometrial cancer from 0.2 to 0.4 % by five additional years of tamoxifen, but previous studies suggest that little if any of this added risk is likely to affect premenopausal women [35••, 37]. Ten-year pulmonary embolism rates were increased from 0.5 to 0.9 % by the extended therapy, but the associated mortality was only 0.2 % in both groups. Younger women are also less likely than those who are at least 60 years old to experience blood clots due to tamoxifen [38]. Thus, because toxicities from extended tamoxifen are relatively minimal (and premenopausal women are less vulnerable to the most serious of these) and because 10 years of tamoxifen improves disease-free and overall survival, many young women may start to pursue longer courses of tamoxifen.

Other new data from the Tamoxifen and Exemestane Trial (TEXT) and Suppression of Ovarian Function trial (SOFT) trials support the safety and possible efficacy of an alternative endocrine therapy approach for premenopausal women utilizing ovarian suppressing medication. Although ovarian function suppression has been explored as a form of endocrine therapy for a long time, the combined phase III randomized trial data from SOFT and TEXT trials (which enrolled 2672 and 3066 premenopausal women with early hormone receptor-positive breast cancer, respectively) provided new evidence that there may be a role for ovarian suppression in combination with aromatase inhibitors in young women at high risk of breast cancer recurrence. On both trials, participants were assigned to 5 years of adjuvant exemestane with ovarian function suppression versus tamoxifen plus ovarian function suppression. The median age from both trials was 43 years old, 42 % of patients had axillary lymph node disease, and 36 % of patients had tumors 2 cm or larger. Chemotherapy was optional. Ovarian function suppression was achieved either using triptorelin or by ovarian radiation or oophorectomy. At 5.7-year median follow-up, exemestane and ovarian function suppression produced significantly better 5-year disease-free survival [91.1 vs. 87.3 %; hazard ratio (HR)=0.72; 95 % confidence interval (CI)=0.60–0.86], 5-year breast cancer-free interval (92.8 vs. 88.8 %; HR=0.66; 95 CI=0.55–0.80), and distant recurrence-free interval (HR=0.78; 95 % CI=0.62–0.97) compared to tamoxifen plus ovarian function suppression. There was no significant difference in overall survival (95.9 vs. 96.9 %; HR=1.14; 95 % CI=0.86–1.51) or in grade 3–4 adverse events (31 % in exemestane plus ovarian function suppression vs. 29 % in tamoxifen plus ovarian function suppression) [39••]. Furthermore, the quality of life analysis of 4096 premenopausal women enrolled in TEXT or SOFT trial showed no overall difference between those receiving tamoxifen and ovarian function suppression versus exemestane and ovarian function suppression. However, patients in the tamoxifen arm tended to have more hot flushes and vaginal discharge while those on the exemestane arm had more arthralgia/myalgia, vaginal dryness, and sexual dysfunction. There was no significant difference between the arms in psychological factors including mood, coping skills, and well-being [40]. Of note, the SOFT trial also included a tamoxifen-only arm, but the results from that arm have not yet been released; we will need to wait for those results before we know whether there is

a benefit from ovarian suppression in this setting. In the meantime, tamoxifen monotherapy remains as the standard of care, but ovarian suppression with either tamoxifen or an aromatase inhibitor may be considered for uncertain benefit in high-risk cases.

Thus, premenopausal women with early-stage estrogen receptor-positive breast cancer now have several options for endocrine therapy based on research to date: (1) 5 years of tamoxifen (likely appropriate for many women with small, node-negative cancers, in whom toxicities of more aggressive therapy may outweigh benefits), (2) 10 years of tamoxifen (likely appropriate for women at somewhat higher risk who are not experiencing substantial toxicities from tamoxifen), and (3) 5 years of ovarian function suppression in addition to either an aromatase inhibitor or tamoxifen (to be considered for high-risk patients who are willing to accept a greater side effect burden). Some high-risk patients may even choose to take tamoxifen monotherapy for five additional years following an initial 5-year course that includes ovarian function suppression, but this approach has not yet been studied for safety and efficacy in the premenopausal population. It is important to note that the long-term cardiovascular impact of ovarian suppression with or without aromatase inhibition in premenopausal women remains to be seen. We await data from the SOFT tamoxifen monotherapy arm as well as from other ongoing and future research to help inform these choices.

Adjuvant Bisphosphonates

Adjuvant bisphosphonates were recently shown to have a significant effect on both distant recurrence (18.4 % in women on bisphosphonates vs. 21.9 % on no bisphosphonates; $P=0.0003$) and bony metastases (5.9 and 8.8 %, respectively; $P<0.00001$) in postmenopausal women in a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group [41]. These benefits were not evident in premenopausal women not receiving ovarian function suppression, but premenopausal women who were receiving ovarian function suppression were grouped with the postmenopausal population. The ABCSG-12 study (included in this meta-analysis) did suggest that 4 mg of intravenous zoledronic acid every 6 months for 3 years may reduce a risk of recurrence in premenopausal women receiving ovarian function suppression with either tamoxifen or an aromatase inhibitor [42••]. Bisphosphonates also may be useful to maintain bone mineral density in young women, though the safety of such an approach in women who have not completed their desired childbearing remains uncertain; theoretically, there could be a detrimental impact of bisphosphonate on a future embryo/fetus because these drugs may remain in the woman's body for many years and could hypothetically leach out of the bones into the bloodstream during a pregnancy and cause fetal skeletal damage.

Physical and Emotional Treatment Sequelae

Menopausal Symptoms

Menopausal symptoms can occur in young women due to treatment-related poor ovarian function or endocrine therapies such as tamoxifen. These symptoms can lead to deterioration of sexual functioning and overall quality of life, with more pronounced issues arising in premenopausal women compared to postmenopausal women [43]. A recent large prospective cohort study surveyed 461 young women 1 year post breast cancer diagnosis about sexual functioning and interest, menopausal symptoms, amenorrhea, and somatic symptoms. Sexual functioning and interest were evaluated using the previously validated Cancer Rehabilitation Evaluation System (CARES) Sexual Functioning Summary Scale, and menopausal/somatic symptoms were assessed using the Breast Cancer Prevention Trial (BCPT) Symptom Checklist [44]. Results showed that women with treatment-related amenorrhea experienced statistically significant decreased sexual interest and increased sexual dysfunction when compared to women without amenorrhea ($P=0.002$). In multivariate analysis, body image, weight issues, and vaginal pain were independently associated with decreased sexual interest. Likewise, vaginal pain, body image problems, and fatigue were independently associated with sexual dysfunction. The study also assessed the role of tamoxifen in sexual functioning and found that it does not adversely affect sexual functioning at 1 year post breast cancer diagnosis [45]. This may be due to the fact that tamoxifen decreases vaginal dryness in some women [46, 47]. This cohort study highlights the importance of addressing treatment-related symptoms and sexual health in young breast cancer patients, as many of these issues are amenable to interventions which can positively affect quality of life.

Distress

Young women diagnosed with breast cancer face unique psychosocial issues and emotional challenges that can produce significant distress (worse than that seen in older breast cancer patients) [43, 48–50]. Younger patients face the possibility of infertility and may suffer more from body image issues, changes in sexual functioning, and strains on relationships with partners and children [51, 52]. One study looking at over 500 breast cancer survivors younger than 50 highlighted that the youngest patients were the most susceptible to depression following diagnosis [53]. Disturbingly, only half of women feel that their concerns are adequately addressed by their physicians [51]. A recent focus group study of 36 young women with breast cancer was conducted to better understand which issues remain unmet. The average age of women in that study was 37.8 years, and the average time since diagnosis was

approximately 2 years. The major themes that emerged were that the participants felt different than older women with breast cancer diagnoses, had difficulty navigating the transition to survivorship, and desired connections both with other survivors and additional professionals including case managers/counselors [48].

Strain on relationships with partners, children, and relatives can be a source of distress for young women with breast cancer. The primary caregiver and source of support for most young women undergoing treatment is their partner. A recent study surveyed 491 women aged <45 years with nonmetastatic breast cancer and their partners to identify differences in perceptions of quality of life between couples during the treatment and active surveillance period. Patients reported greater difficulties with coping, finances, childcare, body image, and sexuality than did their partners. While both patients and their partners felt that support from relatives dwindled over time, partners perceived this loss of support from family more than patients [49, 54].

Infertility

The possibility of infertility is a major concern in many young breast cancer patients [43, 51]. Chemotherapy can cause infertility by direct gonadotoxicity, and years of adjuvant endocrine therapy can indirectly result in infertility because ovarian function naturally wanes over time. Furthermore, attempted pregnancy is delayed because oncologic drugs can cause birth defects. Although approximately half of women diagnosed with breast cancer in their 20s or 30s are interested in maintaining fertility, we have only recently begun to investigate how these desires affect treatment decisions at the time of diagnosis [51, 55, 56]. A prospective study of fertility concerns and decision-making surveyed 620 young women at or under the age of 40 with newly diagnosed early-stage breast cancer and showed that 68 % of women recalled discussing fertility issues with their physician before cancer treatment started and 51 % were concerned about fertility issues at the time of diagnosis. Two thirds of the cohort already had at least one child at the time of diagnosis, 37 % wished to have children in the future, and 10 % underwent fertility preservation (e.g., egg harvesting). Due to these concerns, 1 % chose not to receive chemotherapy, 2 % chose a specific chemotherapy regimen over others, 3 % elected against endocrine therapy, and 11 % considered an abbreviated course of endocrine therapy. In multivariate analysis, the factors associated with fertility concerns included receiving chemotherapy, younger age, nonwhite race, and not having children at time of diagnosis [57•]. Future research will focus on better predictors of infertility after treatment that will help inform young women's decision-making about whether to use fertility preservation techniques and what type of breast cancer treatment best balances efficacy with risk to fertility.

Also, importantly, the standard recommendation for young breast cancer patients interested in future fertility is consideration of egg or embryo cryopreservation prior to systemic therapy. However, the POEMS study, presented at the 2014 American Society of Clinical Oncology Annual Meeting, suggests that the administration of gonadotropin-releasing hormone agonist during chemotherapy may also be useful for protecting fertility in breast cancer patients with hormone receptor-negative disease [58]. Most critically, all young women interested in fertility at the time of a breast cancer diagnosis should be referred to a reproductive endocrinologist as soon as possible to allow consideration of all available options.

Conclusion

Recent exciting advances in the treatment of breast cancer in young women offer hope for improved prognoses in this high-risk group. Over the past year, we have learned that adjuvant ovarian function suppression with aromatase inhibitor therapy may reduce the risk of recurrence in premenopausal patients and that 10 years of tamoxifen is superior to 5 years as adjuvant therapy. New data also now support the use of gonadotropin-releasing hormone agonist therapy for protection of fertility in some patients with estrogen receptor-negative tumors. However, many questions remain with regard to optimal breast cancer treatment and management of treatment sequelae in young women. More research is needed to help individualize therapeutic choices and heighten psychosocial support for this vulnerable population.

Compliance with Ethics Guidelines

Conflict of Interest Raina M. Ferzoco and Kathryn J. Ruddy declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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