Breast Cancer in Young Women (Premenopausal Breast Cancer)

22

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Abstract

Breast cancer in women of childbearing age (premenopausal breast cancer) accounts for almost one-quarter of all breast cancer diagnoses in the United States. Advances in diagnosis and treatment have led to improved outcomes in this population that echo those in the postmenopausal population. Despite these advances, premenopausal women with breast cancer still show a significantly worse prognosis than their postmenopausal counterparts. Differences in presentation, tumor phenotype, and options for therapy may explain some of the difference in outcome. However, research is underway to identify the inherent differences that lead to differential outcomes.

Keywords

Breast cancer • Premenopausal • Young • MRI • Tomosynthesis • Mastectomy • BRCA • Chemotherapy • Endocrine therapy • Prognosis

Introduction

In 2013, over 230,000 new cases of breast cancers will be diagnosed in the United States, and almost 40,000 women will die from breast cancer [1]. Almost one-quarter of new breast cancer cases occur in premenopausal women [2], and substantial improvements in breast cancer outcomes have been achieved over time in younger women [3]. Despite these advances, premenopausal women with breast cancer still exhibit a significantly worse prognosis than their postmenopausal counterparts (Table 22.1) [4].

Prognosis/Clinical Features

Whether younger patients exhibit poorer outcomes due to age alone or because they present with more advanced tumors remains an ongoing research question. Compared with patients older than age 50, younger patients (<35) tend to present

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Table 22.1 Five-year overall survival by age at diagnosis

	Total	Five-year survival				Crude		Adjusted[a]	
Age	No.	Expected	Observed	RSR	95 % CI	RER	95 % CI	RER	95 % CI
20–34	471	99.8	74.7	74.8	70.1–78.9	2.84	2.31–3.49	1.63	1.32–2.01
35–39	858	99.7	83.8	84.1	81.2–86.6	7.16	1.45–2.14	1.08	0.89–1.32
40–49	4,789	99.1	88.3	89.0	88.0–90.0	1.17	1.04–1.31	0.84	0.75–0.94
50–69	15,899	96.8	87.8	90.7	90.1–91.2	1.00	(Ref.)	1.00	(Ref.)

Courtesy of Fredholm et al. [4]
RSR relative survival ratio, *RER* relative excess risks of mortality
[a]Adjusted for year and stage

with significantly larger, multifocal primary tumors with a greater percentage of lymph node positivity. Younger patients also tend to present with tumors that are more commonly estrogen receptor (ER) and progesterone receptor (PR) negative and higher grade, with more lymphovascular invasion (LVI) and greater degrees of tumor necrosis [4–8]. However, in most cases, age remains a significant predictor of poor outcomes even after accounting for these factors [4, 6–8].

Detection

Detection of breast cancer in the premenopausal population can be difficult for numerous reasons. In most countries, women at average risk for breast cancer do not receive screening until age 40. There is little data to suggest any benefit in screening earlier than age 40. Even in patients age 40–49, only statistically nonsignificant improvements in overall survival have been demonstrated [9, 10]. The risk-benefit ratio with respect to true-positive results versus false-positive results and consequent unnecessary biopsy prompted the US Preventative Services Task Force to recommend only biannual screening prior to age 50, if screening is provided at all [11].

With few exceptions, there is an inverse relationship between age and mammographic density. In a study by Checka et al., 74 % of patients between 40 and 49 years old exhibited dense breasts in mammography. This percentage decreased to 57 % of women in their 50s [12]. Increased mammographic density has been associated with difficulty in identifying early breast cancers and has also been described as an independent risk factor for breast cancer [12–14].

Patients at high risk of developing cancer due to genetic mutations, strong family history or personal history of atypia, or Mantle radiation are recommended to undergo earlier screening with alternative methods [15]. The most commonly recommended adjuvant screening test is magnetic resonance imaging (MRI). MRI is far more sensitive in detecting earlier breast cancers, especially in dense breasts. MRI, however, remains inadequate to detect the presence of calcifications and other anatomic variations. Furthermore, its low sensitivity can lead to false-positive screening results and numerous unnecessary biopsies [16–26].

Other alternative screening methods include screening ultrasound and tomosynthesis (also known as "3-D mammography"). Early studies into these imaging modalities as screening methods have met with mixed results [22, 25–29]. Thus far, neither of these methods is considered a primary screening method. The methods are, instead, considered adjuncts to screening [30, 31]. Molecular breast imaging (MBI) or beta-specific gamma imaging (BSGI) has also emerged as a useful screen in the detection of breast cancer. The use of MBI as a screening modality has not been widely studied. However, early trials suggest a benefit from using this technology in combination with mammography [32].

Locoregional Therapy

For most patients with premenopausal breast cancer, effective locoregional therapy does not differ significantly from that provided to postmenopausal

patients. It is generally believed that both breast conservation therapy (BCT) and mastectomy are safe and efficacious in younger patients. However, with decreasing age, the chance of local recurrence increases after BCT [5, 33, 34]. Several studies have found age to be an independent risk factor on multivariate analysis for local recurrence. Despite the increase in local recurrence, whether overall survival is significantly different after recurrence in younger, premenopausal patients remains controversial [33, 35].

Perhaps due to the higher likelihood of local recurrence after breast conservation in the young, the rates of mastectomy are higher in younger patients [36–39]. Tumor size at presentation is also larger in the premenopausal population, which may necessitate mastectomy in some patients. Increased T stage is likely a result of a lack of effective screening in these patients and the biologic aggressiveness of tumors in this population. In addition, decreasing age is an independent predictor for contralateral prophylactic mastectomy (CPM) [36, 40–44]. Although there is currently no evidence that CPM in this population improves overall survival, contralateral disease occurrence is certainly reduced. The surgery is also highly cost-effective when performed in patients age 45–54 [45].

In the event of a BRCA mutation, the benefit of mastectomy and CPM changes. The rate of recurrent or contralateral breast cancer approaches 2–3 %/year for patients with BRCA mutations, compared with 0.5 %/year for the average breast cancer survivor. BRCA patients, especially those with BRCA1 mutations, are more likely to present at younger ages [46]. It has been suggested that patients with breast cancer and a BRCA mutation derive a survival benefit from CPM, although larger-scale studies are needed to confirm these findings [47].

Beyond the debate surrounding surgical therapy of the breast and the contralateral breast, there exists a debate regarding surgical therapy of the axilla in young patients. Traditional staging of the axilla includes a full axillary dissection. Such dissection historically consisted of axilla levels I, II, and III during the radical mastectomy era, followed by the elimination of level III upon the advent of modified radical mastectomy. Oncologists continued to employ axillary dissection after the introduction of breast-conserving therapy. Unfortunately, even with modern axillary dissection, lymphedema rates can range anywhere from 15 % to 30 %.

The 1990s brought the widespread use of the sentinel node biopsy for staging in melanoma. This concept was adopted for use in breast surgery and is now considered the standard of care for axillary staging in the clinically node-negative axilla. Numerous large-scale studies, most notably ACOSOG Z0010 and NSABP B-32, established the equivalence in locoregional recurrence rates between sentinel node and axillary dissection [48–50]. More recently, it has been suggested that for patients undergoing breast conservation and whole-breast irradiation, axillary dissection offers no advantage in terms of locoregional recurrence over sentinel node biopsy in patients who are clinically node negative by physical exam but have one to two sentinel lymph nodes (SLNs) harboring metastatic disease [51, 52].

The application of these changes in patient management has been slow to extend into the premenopausal population, largely due to the low numbers of young women in the large studies that have established equivalent outcomes. However, most large governing bodies, such as the European Society of Breast Cancer Specialists, endorse the limited use of axillary dissection for staging in patients of all ages, including young patients [53].

With respect to adjuvant radiotherapy, there is little difference in the application of this therapy for the young. The risk-benefit ratio appears to remain the same regardless of age. When used in combination with breast conservation or lumpectomy, radiation decreases the risk of recurrence by more than half. However, in the case of postmastectomy radiotherapy (PMRT), the benefit does appear to be greater in young patients, who are thus more likely to receive PMRT for lower stage disease. In the sentinel studies regarding PMRT by the Danish Breast Trialists' Cooperative Group, postmastectomy radiotherapy exhibited a benefit in premenopausal patients with one to two positive lymph

nodes, whereas the benefit of PMRT was demonstrated in postmenopausal patients with >3 positive lymph nodes [54, 55].

Adjuvant Systemic Therapy

Cytotoxic Chemotherapy

The efficacy of adjuvant systemic therapy in improving distant disease-free and overall survival has long been established in both pre- and postmenopausal patients. Such therapy will be discussed elsewhere in this book, and we will therefore concentrate on the implications of systemic cytotoxic chemotherapy on premenopausal patients. Several issues surround the use of chemotherapy in young patients, including premature amenorrhea and its consequences (namely, infertility, osteoporosis, and sexual dysfunction), as well as the use of preoperative (neoadjuvant) chemotherapy in the young.

One of the important issues that surround the treatment of young women with breast cancer is the issue of fertility. Many women delay childbearing until after schooling and beginning careers. In fact, the average age at first birth has risen in most developed countries over the last decade (Fig. 22.1) [56]. Many women who develop premenopausal breast cancer, therefore, have not completed their families and wish to preserve fertility. Unfortunately, many standard chemotherapeutic agents can cause amenorrhea during treatment, which can lead to infertility (Table 22.2) [57]. Even those patients who resume normal menstrual cycles can experience infertility after treatment, mostly due to the cytotoxicity of traditional chemotherapeutic agents towards the declining oocyte pool (Fig. 22.2) [58].

Several approaches can be used to preserve fertility in young cancer patients. The most important component of fertility preservation is to begin frank and open discussion with the patient *before* beginning any systemic therapy. Consideration must be given to the risks and benefits of therapy, such as delay in systemic therapy, the likelihood of infertility after therapy, and the likelihood of success in achieving pregnancy with the current techniques available.

The most traditional form of fertility preservation is embryo cryopreservation, which is endorsed by several organizations, including the European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) in their recent consensus statements [59, 60]. This method provides the best chance of achieving pregnancy after chemotherapy. However, it requires that the patient have a partner with whom she would like to produce children or that she use donor sperm. A newer alternative used with increasing success is oocyte cryopreservation [61]. Both methods require ovarian stimulation, which can be achieved with a number of agents, including letrozole and GnRH agonists [62]. Hormonal stimulation with traditional ovarian stimulators is avoided, as there is limited data on the use of these agents in breast cancer patients. One to two cycles is recommended to improve the likelihood of successful future implantation, and this can delay therapy by as much as 4–6 weeks [63].

An alternative to both of these methods is ovarian tissue harvesting and cryopreservation. This approach is an emerging technology, and extremely limited data/success rates have been reported. At the time of this report, ovarian tissue harvesting and cryopreservation is considered an experimental technique [64, 65].

Another option to be discussed is the use of GnRH agonists during chemotherapy for the protection of ovarian function. Due to the low risk, the practice is largely being used in the premenopausal population, although the data regarding success in preventing infertility and amenorrhea/menopause is variable [66–69].

Randomized trials have demonstrated that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with ER-negative tumors may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea. In patients with ER-positive disease, conflicting results have been reported with respect to the protective effect of GnRH agonist therapy on fertility.

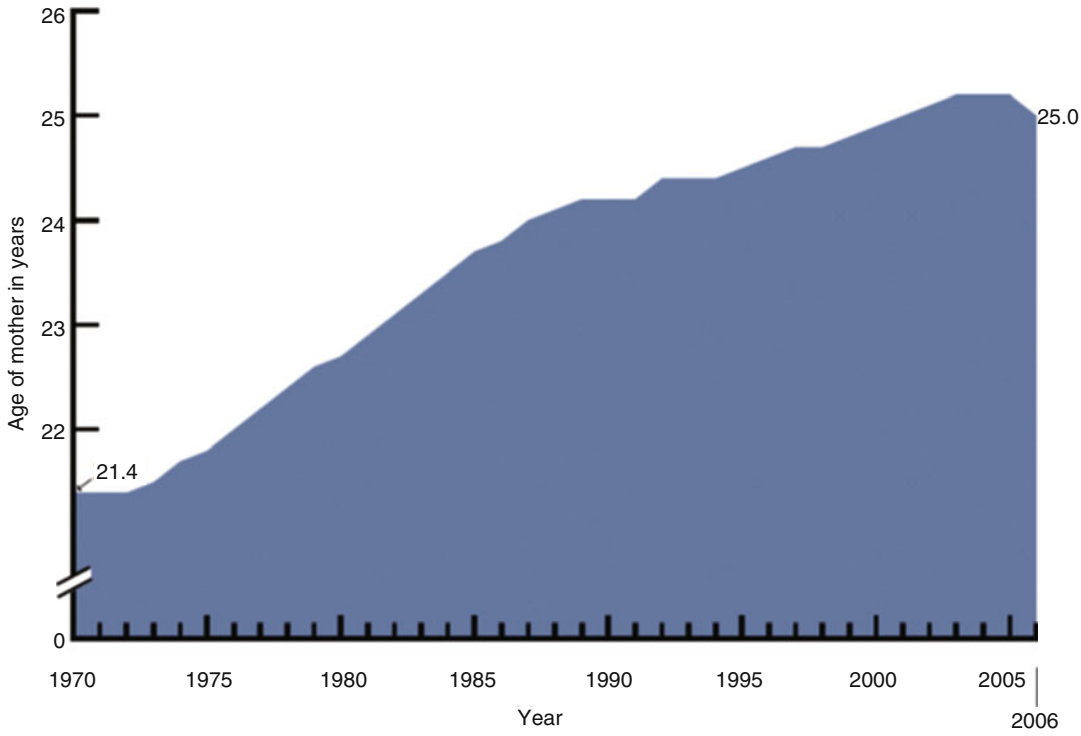

Fig. 22.1 Average age of mother at first birth, United States 1970–2006 (Courtesy of the Centers for Disease Control, CDC/NCHS, National Vital Statistics System)

Table 22.2 Incidence of amenorrhea with chemotherapy

Adjuvant chemotherapy	Incidence of amenorrhea
CMF	61 % (<40 year)
	95 % (≥40 year)
AC	34 %
FAC	32.8 %
TAC	51.4 %
Doxorubicin based	59 %
CEF	51 %

Courtesy of Minton and Munster [57]
CMF cyclophosphamide, methotrexate, 5FU; AC doxorubicin, cyclophosphamide; FAC 5FU, doxorubicin, cyclophosphamide; TAC docetaxel, doxorubicin, cyclophosphamide; *CEF* cyclophosphamide, epirubicin, 5FU

In addition to infertility, premature menopause associated with chemotherapy can cause a host of other problems, including sexual dysfunction and osteoporosis. Sexual dysfunction can be a problem after diagnosis as well as during and after therapy and can affect both pre- and postmenopausal women. Recent evidence suggests that younger women and their partners can have greater problems with intimacy [70]. In a study performed by Alder et al., it was noted that while the only predictor for desire was the quality of the relationship, chemotherapy was predictive for problems with arousal, lubrication, orgasm, and sexual pain [71]. Treatment is typically targeted at symptom management for physical dysfunction with lubrication, for which it includes local estrogen therapy, especially in patients with a history of hormone receptor-negative disease, and it is targeted at psychological/family therapy for intimacy issues [72–74].

Osteopenia/osteoporosis can be induced by premature menopause due to the acute and premature withdrawal of estrogen, which supports bone mineral density [75, 76]. The use of tamoxifen can increase bone density in postmenopausal women, but tamoxifen decreases bone density in premenopausal women, so it is quite difficult to assess its true impact on patients with chemotherapy-induced menopause

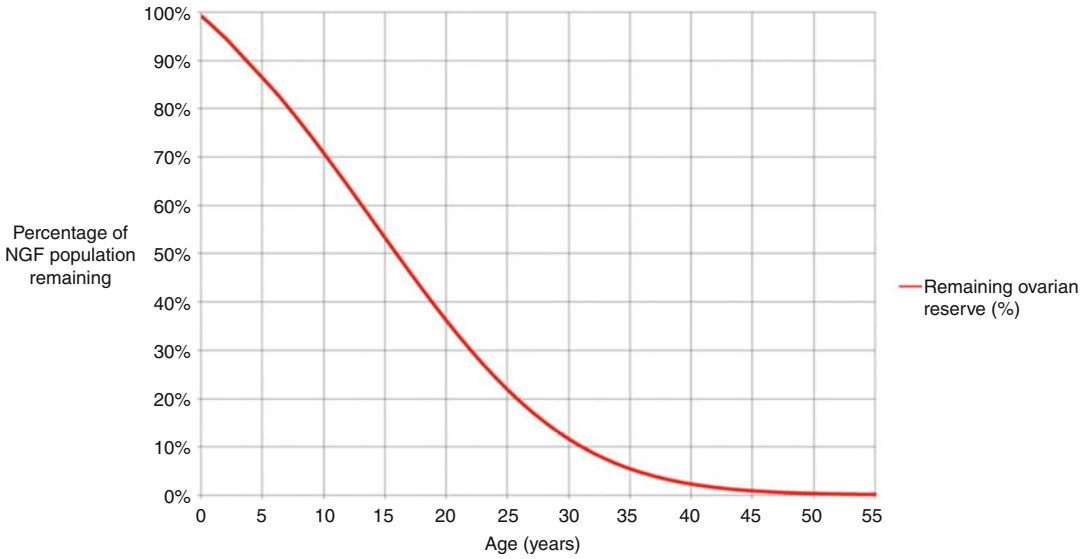

Fig. 22.2 Human female oocyte reserve by age (years) (Courtesy of Wallace and Kelsey [58])

[77]. Supplementation with calcium and vitamin D is recommended, as well as maintaining moderate physical activity with weight-bearing exercise, just as is recommended for those at risk for standard postmenopausal bone loss.

Bisphosphonates have also been used for the last decade to treat osteoporosis, and their effect on chemotherapy-related bone loss is now being widely studied. Studies involving large cohorts of women both in North America and Asia have reported that zoledronic acid can ameliorate bone loss in premenopausal patients undergoing cytotoxic chemotherapy, with its effects lasting at least 1 year [78–81].

Neoadjuvant Chemotherapy

The concept of preoperative or neoadjuvant chemotherapy for the treatment of locally advanced breast cancer is well studied. There are several known indications for neoadjuvant chemotherapy, including converting an inoperable tumor to an operable one and converting a mastectomy candidate into a breast conservation candidate.

For various reasons, neoadjuvant chemotherapy is often used in the treatment of premenopausal women with breast cancer. Typically, as noted previously, younger women present with more advanced disease, which may benefit from downstaging. These women also typically exhibit a greater preponderance of hormone receptor-negative and/or HER2-positive disease, both of which would otherwise require adjuvant chemotherapy and are more likely to respond to neoadjuvant chemotherapy [82, 83] (Fig. 22.3). Additionally, even within specific tumor subtypes, premenopausal women are more likely to demonstrate a pathologic complete response to therapy than their postmenopausal counterparts [84].

Endocrine Therapy

Despite the extensive research noted previously, the optimal systemic therapy for premenopausal women remains elusive. Questions remain regarding the type and duration of endocrine therapy. Moreover, information about the value of ovarian suppression/ovarian ablation (OS/OA) continues to emerge, but it remains unclear whether the addition of such strategies to tamoxifen and chemotherapy is necessary.

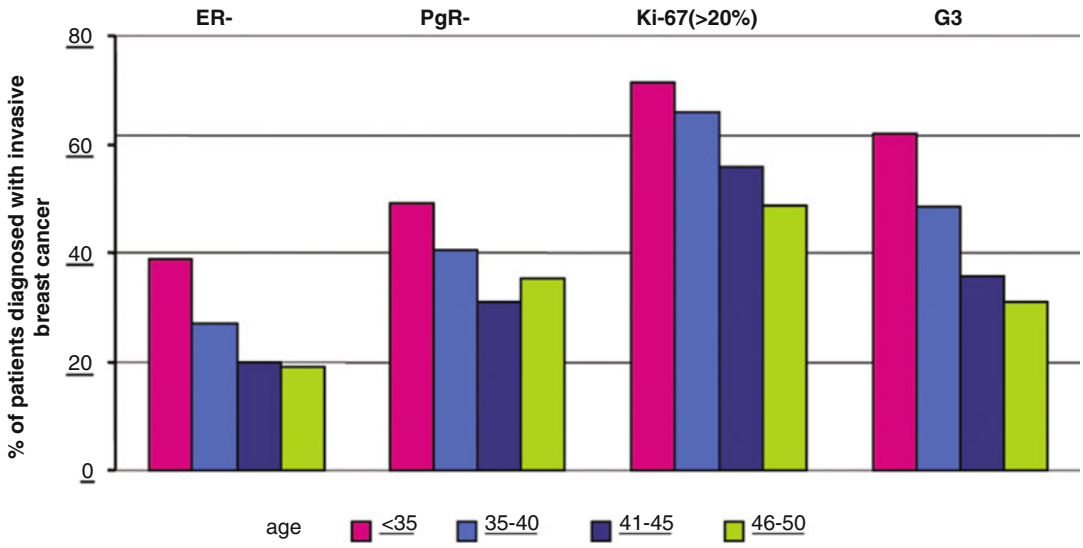

Fig. 22.3 Variation in immunohistochemical subtype by age [83]

Ovarian Ablation or Ovarian Suppression

Both OA and OS have been shown to improve survival in patients with early-stage breast cancer. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview, also known as the Oxford Overview, represents a meta-analysis of the existing trial data of adjuvant therapy with tamoxifen, chemotherapy, and OA/OS. The most recent overview on ovarian ablation for breast cancer contained data from almost 8,000 women ≤50 years of age with either ER-positive or ER-unknown disease who were randomized into trials of OA [85]. OA and OS both reduced recurrence and breast cancer mortality, but this occurred only in the absence of other systemic treatments.

Opinions regarding the efficacy of the combined use of OS/OA alone or in combination with endocrine therapy and chemotherapy in premenopausal patients have varied over the last several years, with much conflicting data. As recently as 2011, the American Society of Clinical Oncology (ASCO) endorsed the Cancer Care Ontario practice guidelines on adjuvant OS/OA in the treatment of premenopausal women with early-stage breast cancer [86]. The opinion of both groups, based on the preponderance of available data, was as follows: "OA should not be routinely added to systemic therapy with chemotherapy, tamoxifen, or the combination of tamoxifen and chemotherapy." The guidelines also recommended against using OA as an alternative to other systemic therapy, providing that the patient was a candidate for other systemic therapy.

More recently, analysis of the Austrian Breast and Colorectal Cancer Study Group trial-12 (ABCSG-12) at the 62-month follow-up reported outcomes in premenopausal, early-stage patients receiving goserelin who were randomized to anastrozole or tamoxifen with or without zoledronic acid. Investigators observed improved disease-free survival (DFS) in patients taking zoledronic acid with anastrozole or tamoxifen [87], but the difference lost statistical significance when measuring the anastrozole arms separately. Overall, the outcomes of the ABCSG-12 trial are excellent, with >96 % of patients alive at the 62-month follow-up, despite the facts that 31 % of the patients were node-positive and that only 5.4 % of patients received chemotherapy.

As evidenced above, much has been written about combined pharmacologic ovarian OA/OS

and endocrine therapy in the premenopausal population, but few recent studies have addressed surgical ovarian ablation and endocrine therapy. Ovarian ablation by oophorectomy can be a cost-effective alternative to pharmacologic ovarian suppression, especially in economically disadvantaged areas of the world. In combination with tamoxifen, ovarian ablation by oophorectomy provides equivalent DFS and overall survival for a fraction of the cost [88]. Previous reports have suggested that variations in the hormonal milieu related to the menstrual cycle may affect the short-term DFS and overall survival (3.6-year median) associated with oophorectomy and tamoxifen [88, 89].

Neoadjuvant Endocrine Therapy

Despite the wide acceptance of neoadjuvant endocrine therapy in the postmenopausal population [90], neoadjuvant endocrine therapy in the premenopausal population with or without ovarian suppression remains controversial [91]. Early studies reported the use of tamoxifen, buserelin, or both in premenopausal women with metastatic or locally advanced breast cancer [92, 93].

The only prospective randomized trial of neoadjuvant endocrine therapy in premenopausal women, the Study of Tamoxifen or Arimidex plus Goserelin Acetate to Compare Efficacy and Safety (STAGE), evaluated goserelin plus either anastrozole or tamoxifen for 24 weeks prior to surgery [94]. This Japanese study found that the likelihood of a complete or partial response was significantly higher in the anastrozole group. These results appear to be in direct opposition to those from ABCSG-12, in which tamoxifen plus goserelin led to better overall survival. However, the authors of this study noted that this effect in ABCSG-12 was only observed in a subset of patients with body mass index (BMI) higher than 25 kg/m^2. The percentage of patients with a BMI $\geq$25 in the ABCSG-12 study was nearly twice that of the STAGE trial (33.0 % vs. 17.3 %). This discrepancy may explain the improved efficacy of anastrozole in comparison with tamoxifen in the STAGE trial but may also raise questions as to whether these results can be extrapolated to Western populations, where BMI is typically higher (as seen in ABCSG-12).

Duration of Adjuvant Endocrine Therapy in Premenopausal Women

The question of the duration of adjuvant endocrine therapy in premenopausal women is highly important. The NSABP B14 extension study randomized over 1,100 premenopausal patients to either placebo or tamoxifen after completing 5 years of adjuvant tamoxifen therapy. Seven years of follow-up showed a slight advantage in patients who discontinued tamoxifen relative to those who continued to receive it [95, 96]. These findings, along with concern for cumulative toxicity with ongoing tamoxifen, previously established 5 years of adjuvant tamoxifen therapy as the standard of care for premenopausal women.

However, recently, an analysis of the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial, which included almost 13,000 women with early breast cancer who had completed 5 years of treatment with tamoxifen and then were randomly allocated to continue tamoxifen for 10 years or to stop at 5 years, reported improved recurrence and mortality rates with continuation of tamoxifen [97]. The mortality reduction was only significant after year 10.

ATLAS and other studies have reported mild to serious side effects with endocrine therapy, including hot flashes, night sweats, irritability, insomnia, and weight gain, as well as other more serious issues of uterine cancer and complications from hypercoagulability. Extended treatment with 10 years of tamoxifen can yield a significantly increased risk of uterine and pulmonary embolus, but there appears to be no increase in stroke, and ischemic heart disease can be decreased.

The challenge, however, lies in the determination of appropriate timing for switching premenopausal women who become postmenopausal during their first 10 years on tamoxifen to an aromatase inhibitor. The MA17 study demonstrated that extended adjuvant therapy with 5 years of

letrozole after 5 years of tamoxifen improved relapse rates and survival [98]. Because there are no comparisons between such sequencing strategies and 10 years of tamoxifen treatment, it remains unknown whether switching to an AI after 2–3 years of tamoxifen (or vice versa) or switching to an AI after 5 years of tamoxifen would be superior to 10 years of tamoxifen alone.

Conclusion

Breast cancer is a common disease among women, and it is complex and can be difficult to treat. Premenopausal breast cancer presents a special challenge; the disease can be difficult to detect and can require alterations in therapy due to more aggressive disease, risks of therapy, and the effect on the young patient's life. Much is known about local and systemic therapy in this population, but research to define the special needs of premenopausal breast cancer patients is ongoing.

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