Breast Cancer in Women Under 40

Review Article | May 14, 2009 | Oncology Journal, Breast Cancer
By Jeffrey Peppercorn, MD, MPH

Breast cancer is the most common cancer in women, with over 180,000 new diagnoses of invasive disease annually in the United States, based on recent estimates.[1] Despite advances in therapy, over 40,000 women still die of breast cancer each year in the US.[1] While most women with breast cancer present with early-stage, potentially curable disease, young women face higher risks of recurrence and death compared to older women, which leads to challenges in selecting the optimal treatment strategy for these patients. The clinician is typically confronted with an otherwise healthy patient facing a life-threatening disease, and we are inclined to offer therapies with maximal benefit and minimal longterm toxicity, in the face of frequently inadequate or evolving data on how to achieve this.

This manuscript will review the challenge of managing breast cancer in women under 40 years old, the therapeutic choices facing us in the clinic, and emerging data from recent clinical trials.

Is Breast Cancer in Women Under 40 a Different Disease?

Given an otherwise similar cancer presentation, should women under 40 be treated differently from older women on the basis of age alone? The answer is not entirely clear. Even the age range that should be viewed as being at higher risk is somewhat controversial, with women under 35, 40, or 45 classified as “young” in different studies.[2-4] While breast cancer in women under 40 is rare, accounting for roughly 6.5% of all cases, it is more likely to be associated with high-risk features than the cancers seen in older women.[5] In addition, breast cancer in women under 40 may signal a BRCA mutation—and testing should be considered in all young patients— but for most young women a specific etiology is not identified.

Breast cancers in young women are more likely to be estrogen receptor-negative and of higher grade.[6,7] Several studies suggest that HER2-positive disease is more common in younger women.[2,8] In addition, young African-American women are more likely to have triple-negative breast cancer (estrogen receptor-negative, progesterone receptor-negative, and HER2-negative) compared to older women and to young Caucasian women.[9] Age also appears to play a role in risk of recurrence, independent of other disease features.[10]

A recent study by Anders and colleagues suggests that there may be biologic pathways common to tumors from women under 45 compared to those from women over 65.[2] This research identified differential expression within sets of genes related to cell signaling, survival, immune function, and other possible correlates of tumor pathogenesis that appeared to distinguish tumors in younger women from those in older women. Further investigation is needed to clarify whether any ofthese differences represent a specific high-risk feature of cancers prevalent in younger women but present in some older women vs a common process in all younger women with breast cancer. The latter possibility would suggest a need to view breast cancer in this population as a distinct breast cancer subtype.

At a minimum, it is clear that there are as yet unidentified biologic factors contributing to a higher risk of recurrence for young women with breast cancer. Even if these factors are neither present in all cancers in younger women nor confined to this age group, they still require us to consider more
rather than less treatment for this patient population. When appropriate, we also need to discuss emerging treatment strategies and/or participation in clinical trials with these patients. This bias toward what many call “aggressive” treatment should, however, be tempered by the fact that women under 40 are also at higher risk for long-term consequences of initial treatments, and for many of our interventions the side effects 20 years and farther down the road are unknown.

**Endocrine Therapy and Other Options**

**TABLE 1**

Considerations for Systemic Therapy in Young Women With Endocrine Receptor–Positive Breast Cancer

For premenopausal women with early-stage endocrine receptor–positive disease, standard therapy includes tamoxifen for 5 years. This strategy is supported by an analysis from the Early Breast Cancer Trialists’ Collaborative Group suggesting a 47% improvement in disease-free survival compared to no endocrine therapy, and a sustained improvement in overall survival of approximately 30% at 15 years, regardless of age.[11,12] Deferring for a moment the challenging question of chemotherapy, major questions for young women with endocrine receptor–positive breast cancer include: (1) How long should we continue tamoxifen? (2) Should we add ovarian suppression? (3) Is the use of aromatase inhibitors plus ovarian suppression superior to tamoxifen plus ovarian suppression? (4) Should we conduct CYP2D6 testing for tamoxifen metabolism? and (5) Should we add adjuvant bisphosphonate therapy (Table 1)?

**Duration of Treatment**

The standard of tamoxifen for 5 years is based on studies comparing 5 years to 1 or 2 years of therapy, finding 5 years superior in terms of disease-free and overall survival.[12] In addition, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial randomized over 1,000 women with endocrine receptor–positive, lymph node–negative breast cancer completing 5 years of tamoxifen to 5 additional years of therapy vs placebo, and found no difference in outcomes, regardless of age.[13]

Two large studies—the adjuvant Tamoxifen Treatment offer more (aTTom) and Adjuvant Tamoxifen Longer Against Shorter (ATLAS) trials—are continuing to explore the optimal duration of tamoxifen therapy. Although both trials are complicated by a pragmatic community- based design, variable initial duration of tamoxifen therapy, and unclear endocrine receptor status for some patients, these trials will provide data on close to 20,000 patients randomized to stopping tamoxifen (at 4 to 5 years for most patients) vs 5 additional years of therapy.

To date, with roughly 7,000 patients, the aTTom trial demonstrates no significant difference in recurrence risk for 10 vs 5 years of tamoxifen, but a small increase in the risk of endometrial cancer with longer therapy.[14] On the other hand, in a preliminary report of the ATLAS trial, results from over 11,000 patients showed a small benefit in disease-free survival but no difference in overall survival.[15]. At this time, the standard duration of therapy remains 5 years, and further data from these large trials are anticipated. Pending these results, it is reasonable to discuss the pros and cons of additional years of treatment and the limits of data in this area with individual patients who face a high risk of recurrence.

**THE ISSUES**

- Does breast cancer in women under 40 merit a different approach to therapy?
How do we balance reduction of recurrence risk and long-term effects of treatment among young women with breast cancer?

What steps beyond standard therapy merit consideration in young women at highest risk?

For patients at highest risk of recurrence who experience permanent amenorrhea due to chemotherapy, clinicians should consider the data from the MA.17 trial showing reduction in recurrence risk from 5 years of letrozole (Femara), an aromatase inhibitor (AI), following 5 years of tamoxifen.[16] This trial included women rendered postmenopausal due to chemotherapy or ovarian ablation; some form of ovarian ablation/suppression or frequent monitoring of menopausal status should be implemented if AI therapy is pursued.[17]

Should We Add Ovarian Suppression?

Ovarian suppression is one of the oldest known therapies for breast cancer.[18] The benefits of ovarian suppression alone have been reviewed previously.[19] Whether the addition of ovarian suppression to tamoxifen is more beneficial than tamoxifen alone is currently unclear.[20] This question is being addressed in the Suppression of Ovarian Function Trial (SOFT), in which patients are randomized to tamoxifen, tamoxifen plus ovarian suppression, or an AI plus ovarian suppression; the design of this trial reflects the clinical uncertainty in this area. Several randomized clinical trials, including the ongoing Tamoxifen/Exemestane Trial (TEXT) and the recently reported Austrian Breast Cancer Study Group (ABCSG) 12 trial,[21] have adopted ovarian suppression plus tamoxifen as the standard control arm for comparison with ovarian suppression plus an AI. Patients who experience temporary or permanent amenorrhea secondary to chemotherapy have a lower risk of recurrence than patients who experience no cessation in menses, and this difference has long been attributed to the endocrine effects of chemotherapy.[22] Presumably, a similar benefit should be seen through administration of ovarian suppression. There is both a greater rationale for administration of ovarian suppression among young women who may not experience the endocrine benefits of chemotherapy, and reason for caution and concern with the quality of life and late effects of early menopause in these patients. Routine use of ovarian suppression among young women with endocrine receptor–positive breast cancer is not recommended, but this author considers it a reasonable topic for discussion and consideration in select patients at high risk for recurrence.[20,23]

Is an AI-Based Strategy Superior to Tamoxifen?

Although AIs are a standard component of adjuvant endocrine therapy for postmenopausal women, their role in adjuvant therapy for younger women, if any, remains unclear. There may be important biologic differences between cancers that arise in pre- and postmenopausal settings and differences in the effect of further estrogen deprivation (above and beyond ovarian suppression), as opposed to estrogen receptor blockade with tamoxifen. As noted above, the SOFT and TEXT trials will address this question. Recent data from the ABCSG 12 trial found no benefit for ovarian suppression plus an AI vs ovarian suppression plus tamoxifen. Thus, tamoxifen remains the standard.[21] For young women with endocrine receptor–positive disease who are unable to tolerate tamoxifen or who have a strong contraindication to such therapy, treatment with an AI plus ovarian suppression can be considered a reasonable alternative. The lack of differences in the ABCSG trial is reassuring, although the study was not powered for noninferiority.

Some women will develop permanent or prolonged amenorrhea after treatment with chemotherapy, but AIs may increase the likelihood of ovarian recovery, making concurrent treatment with ovarian suppression—or, at minimum, frequent monitoring of menopausal status—important.[24]

Case Report: A Young Woman Who Wants to ‘Do Everything’ to Reduce Her Recurrence Risk

Mrs. S. is a 37-year-old woman who noted a left breast mass. Mammography confirmed a 1.2-cm mass, and ultrasound-guided biopsy revealed a grade 2 infiltrating ductal carcinoma with no lymphovascular invasion. She underwent a left-sided simple mastectomy revealing 1.2 cm of grade 2 invasive disease associated with grade 3 ductal carcinoma in situ, prophylactic contralateral mastectomy with no disease on the right, and bilateral sentinel lymph node dissection revealing one positive lymph node on the left. Subsequent left axillary dissection revealed one additional positive lymph node, for a total of 2/20 involved. The tumor was estrogen receptor–positive, and HER2-negative by immunohistochemistry (1+).
The patient is seen by the medical oncologist and explains that she wants to “do everything” to reduce her risk of recurrence, but she does not want to participate in a clinical trial at this time.

What are the options for her therapy?
1. Dose-dense AC-T, followed by 5 years of tamoxifen
2. TC, followed by 5 years of tamoxifen and bilateral oophorectomy
3. Dose-dense AC-T, followed by 5 years of tamoxifen, followed by 5 years of an aromatase inhibitor with ovarian suppression
4. Bilateral oophorectomy and 5 years of tamoxifen, followed by 5 years of an aromatase inhibitor
5. Tamoxifen and ovarian suppression × 5 years, plus zoledronic acid for 3 years
6. TC, CYP2D6 testing to guide tamoxifen vs ovarian suppression plus aromatase inhibitor therapy
7. Multigene assay for recurrence score to determine need for chemotherapy, plus 5 years of tamoxifen

Any of the above options can be supported by some published data, but with varying degrees of top-quality evidence, and no single answer above would qualify as “doing everything.” That said, the author would prefer options 1 or 2.

**Should We Perform CYP2D6 Testing?**

One additional factor to consider is the patient’s ability to metabolize tamoxifen. Tamoxifen is metabolized to endoxifen, a more potent binder of the estrogen receptor, by the cytochrome P450 enzyme CYP2D6.[25] Differences in CYP2D6 genotype lead to differences in endoxifen levels and correlate with breast cancer recurrence risk among women treated with tamoxifen.[25,26] Therefore, some authors advocate testing all patients for CYP2D6 prior to starting tamoxifen, and choosing an alternative endocrine strategy for poor metabolizers.[27]

Testing at this time, however, remains controversial.[28] While some favor testing only those who demonstrate few or no hot flashes on tamoxifen, the strength of the association between symptoms and CYP2D6 status has recently been challenged.[29] At this time, evidence in the area of CYP2D6 testing is emerging, and while tamoxifen metabolism appears to have an impact on recurrence risk, it is not yet clear if an alternative strategy is superior for young women with breast cancer.

Data on the benefits of CYP2D6 testing among postmenopausal women will likely be forthcoming from analysis of pharmacogenetic data and outcomes in one or more of the large adjuvant trials comparing tamoxifen to AIs, but we will need to use caution extrapolating these data to the premenopausal setting. One immediately useful detail to arise from this line of investigation is the recognition that many of the commonly used antidepressant medications—in particular, selective serotonin-reuptake inhibitors (SSRIs)—can block metabolism of tamoxifen by CYP2D6, rendering some patients with endoxifen levels similar to what is seen in those with a genetically poor metabolism status.[30] Several antidepressants, such as venlafaxine (Effexor), appear to be safe in this regard, but the majority of drugs in this class should be avoided among young women on tamoxifen.

**Should We Add Adjuvant Bisphosphonate Therapy?**

Young women with breast cancer face the possibility of bone density loss and early osteoporosis from a variety of factors. Loss of ovarian function—either due to direct ovarian therapy such as an luteinizing hormone-releasing hormone (LHRH) analog or oophorectomy, or as an indirect effect of chemotherapy—has been shown to reduce bone density.[31] Even tamoxifen alone, which increases bone density in postmenopausal women, has a negative impact on bone density among premenopausal women.[32,33]

Adjuvant bisphosphonate therapy has been shown to reduce the risk of bone loss in several randomized, controlled trials, though the impact on important clinical outcomes like fracture risk are less clear.[34,35] The primary question is whether an adjuvant bisphosphonate can reduce the risk of cancer recurrence. This concept is not new. In 1998, Diel and colleagues found that 2 years of adjuvant oral clodronate improved disease-free survival, reducing the risk of both bone and visceral metastases among premenopausal women at high risk for recurrence.[36] However, subsequent studies failed to confirm these results, suggesting that adjuvant clodronate might actually increase the risk of visceral metastases, or that any benefits in terms of reduced bone metastases were confined to the period of treatment and not sustained.[37,38]
Interest in adjuvant bisphosphonates was recently revived by the ABCSG 12 trial, which, in addition to evaluating the question of optimal endocrine therapy, randomized approximately 1,800 premenopausal women to zoledronic acid (Zometa) every 6 months for 3 years vs no zoledronic acid.[21] Only 5% of the women in this study received neoadjuvant chemotherapy, and no participants received adjuvant chemotherapy. Thus, the study primarily addressed the benefit of zoledronic acid when added to endocrine therapy. The investigators observed a significant improvement in disease-free survival (hazard ratio = 0.64; 95% confidence interval = 0.46–0.91; \( P = .01 \)), with a reduction in both bone metastases and visceral metastases, as well as a reduced risk of local recurrence. In addition, every-6-month zoledronic acid proved safe and well tolerated, with few serious events (although increased arthralgia and bone pain) and no cases of jaw osteonecrosis or renal failure.

On the strength of this study, I will consider adjuvant zoledronic acid for high-risk patients treated with endocrine therapy alone (which would typically apply only to patients with major contraindications to chemotherapy, or patients declining chemotherapy). However, this is a single study, which did not address the benefit of adjuvant bisphosphonates among young women receiving chemotherapy. Further trials in this area are clearly needed, and data are anticipated from the AZURE trial (Does Adjuvant Zoledronic acid redUce REcurrence in patients with high-risk localised breast cancer?), which included women with stage II/III breast cancer receiving chemotherapy and/or endocrine therapy.

### Do All Young Women With Breast Cancer Require Chemotherapy?

<table>
<thead>
<tr>
<th>For Endocrine Therapy</th>
<th>For Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen alone</td>
<td>Concurrent or sequential anthracycline- and taxane-based therapy for high-risk patients</td>
</tr>
<tr>
<td>Extended duration of tamoxifen or alternative endocrine therapy</td>
<td>Anthracycline- or taxane-based therapy for lower-risk patients</td>
</tr>
<tr>
<td>Addition of ovarian suppression/ablation</td>
<td></td>
</tr>
<tr>
<td>Use of CYP2D6 testing</td>
<td></td>
</tr>
<tr>
<td>Adjuvant bisphosphonate therapy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>For HER2-Targeted Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracycline- or non-anthracycline- based trastuzumab-containing regimen</td>
</tr>
</tbody>
</table>

Given that young women with breast cancer tend to be otherwise healthy (able to tolerate therapy) and face a higher risk of recurrence, there is frequently a strong rationale for administering chemotherapy. For triple-negative patients, chemotherapy is the only proven effective systemic therapy, and for HER2-positive patients, chemotherapy is standard in all regimens. For endocrine receptor-positive patients, age is often a factor that moves physicians and patients toward chemotherapy.

However, several studies have shown that tumor biology as predicted by multigene assays can predict risk of recurrence better than traditional prognostic factors, including age, and may also predict response to chemotherapy.[39,40] For patients with low (and possibly even intermediate) risk of recurrence, Paik and colleagues found minimal to no benefit from additional treatment with CMF (cyclophosphamide, methotrexate, fluorouracil [5-FU]) chemotherapy, in contrast to small benefits predicted by traditional models.[41]

Ongoing studies are addressing the predictive value of the 21-gene recurrence score (the Trial Assigning Individualized Options for Treatment [Rx], or TAILORx) and the Amsterdam 70-gene panel (the Microarray in Node-Negative Disease May Avoid Chemotherapy Trial, or MINDACT) for modern chemotherapy regimens, with patients at intermediate risk randomized to chemotherapy vs no chemotherapy. At this time, testing for biologic recurrence risk using one of these commercially available multigene assays, or within a clinical trial, is appropriate for young women with lymph node-negative, endocrine receptor-positive breast cancer.

This approach may also have value among patients with lymph node-positive disease. It appears likely that biology, as determined by these genetic tests, will prove to be a major predictor of response and benefit from adjuvant chemotherapy, but further data are needed, given the relatively high risk of recurrence (approximately 40% in one study) even for patients classified as low risk.[42]
Selection of Chemotherapy

Several choices confront the clinician considering chemotherapy regimens in this setting. First, one must consider whether to use a more or less intensive regimen in terms of duration of therapy and combination/sequencing of chemotherapeutic agents, and second, there is the question of precisely which regimen to use. For patients at greatest risk of recurrence—for example, those with multiple positive lymph nodes or those with triple-negative breast cancer, for whom chemotherapy is the only effective systemic therapy—several third-generation regimens offer large reductions in risk of recurrence through the addition of a taxane to an anthracycline-based regimen. For patients at lower risk of recurrence, either anthracycline-based or taxane-based chemotherapy might be appropriate.

### TABLE 2

Select Chemotherapy Regimens for Consideration in Young Women With Breast Cancer

With regard to the more intensive regimens, common considerations include (1) dose-dense chemotherapy with AC (doxorubicin [Adriamycin] and cyclophosphomide) followed by paclitaxel (AC-T), (2) FEC (5-FU, epirubicin [Ellence], and cyclophosphomide) followed by docetaxel (FEC-D), or (3) TAC (docetaxel [Taxotere], doxorubicin, and cyclophosphomide). All have proved superior to non-anthracycline-containing regimens in large phase III randomized trials, and have not been compared directly to each other, making any of the above an acceptable choice of therapy (see Table 2).[20]

Both Cancer and Leukemia Group B (CALGB) 9344 and NSABP B-28 demonstrated improvements in disease-free survival of approximately 17% with four cycles of AC followed by four cycles of paclitaxel, compared to four cycles of AC alone, although a survival benefit was seen only in CALGB 9344.[43, 44] Further incremental improvement was identified in CALGB 9741, in which AC-T on an every-2-week basis with granulocyte colony-stimulating factor (G-CSF, Neupogen) support proved superior to every-3-week therapy, with a 24% improvement in disease-free survival and a 31% improvement in overall survival.[45]

Similarly, in the PACS 01 trial, FEC-100 (where 100 represents the dose in mg/m² of epirubicin) followed by three cycles of docetaxel yielded significant improvements in disease-free survival (increased by 17%) and overall survival (increased by 27%) compared to six cycles of FEC-100.[46]

While febrile neutropenia rates were higher for patients on FEC-D (11.2 vs 8.4%), nausea and vomiting was greater with six cycles of FEC (20.5% vs 11.2%). Overall, the rates of serious adverse events were comparable between regimens.

### RECOMMENDATIONS

- Develop a risk-based strategy for treatment and discussion of options with young women with breast cancer.
- Consider the addition of ovarian suppression and adjuvant bisphosphonate therapy, particularly for young women receiving endocrine therapy alone.
- Discuss with patients the relevant data for reduction in risk of recurrence, short- and long-term toxicities from therapy (including fertility issues), and the limitation of available data, and allow patients to make informed collaborative decisions regarding therapy.

Finally, in the Breast Cancer International Research Group (BCIRG) 001 trial, patients with positive lymph nodes were randomized to six cycles of TAC vs six cycles of FAC. TAC provided a 28% disease-free survival improvement (75% vs 68% at 5 years), and a 30% improvement in overall survival. TAC caused markedly greater hematologic toxicity, with approximately 25% of patients developing febrile neutropenia compared to 2.5% with FAC. In addition, the researchers reported greater asthenia with TAC (11.2% vs 5.6%), but TAC was less emetogenic than FAC.[47] The relative efficacy of concurrent anthracycline and taxane vs sequential anthracycline followed by taxane remains unknown, and any of the above, as well as several similar regimens (such as AC followed by docetaxel or weekly paclitaxel), are acceptable. Recent data from NSABP B-30 suggest
that the sequential strategy may be superior, but both approaches appeared equivalent in BCIRG 005, and longer follow-up is required to address this question.[48, 49]

For patients at lower risk of recurrence, AC alone remains a standard chemotherapy option. However, in a large randomized trial, Jones et al compared four cycles of AC to four cycles of TC (docetaxel plus cyclophosphomide). TC proved superior in terms of both disease-free survival and overall survival, and is an acceptable alternative to AC for patients with 0 to 3 involved lymph nodes.[50] As a nonanthracycline regimen, TC has the advantage of posing a lower risk of life-threatening cardiomyopathy and leukemia, but is also associated with a higher risk of febrile neutropenia. The ongoing CALGB 40101 trial, which is comparing AC vs paclitaxel alone, will help further address the issue of taxane- vs anthracycline-based regimens for patients at lower risk of recurrence.

Selection of Therapy for Young Women With HER2-Positive Disease

For patients with HER2-positive breast cancer, the use of adjuvant trastuzumab (Herceptin) has dramatically altered expected outcomes of standard therapy.[51] The primary questions now facing clinicians are which trastuzumab-based regimen to select, and how small a tumor to consider for systemic therapy.

With regard to chemotherapy, the major decision is whether to administer an anthracycline-containing regimen. This is also a concern in older patients, who are at higher risk of cardiac toxicity. In the young patient, we not only wish to avoid a potentially life-threatening toxicity, but we face conflicting impulses of another sort: While we would like to pursue maximal therapy with a class of drugs long considered the most effective for breast cancer, we must be careful to avoid any factor that might prevent the patient from seeing the full benefit of trastuzumab. We are currently without data to determine the best approach.

The benefit of adjuvant trastuzumab was first demonstrated in the combined analysis of NSABP B-31 and North Central Cancer Treatment Group (NCCTG) N9831, in which AC-T was compared to AC-T plus concurrent trastuzumab (AC-TH), given initially in combination with paclitaxel for 12 weeks, and then continued for a total of 1 year of trastuzumab therapy.[52] Compared to AC-T alone, AC-TH resulted in a 52% improvement in disease-free survival and 33% improvement in overall survival. The primary problem with AC-TH was a 2.9% to 4.1% incidence of severe cardiac toxicity or cardiac death. Furthermore, because treatment started with an anthracycline, 6% of patients experienced a decline in ejection fraction and were unable to receive any trastuzumab therapy, and roughly 20% were unable to complete 1 year of therapy as planned due to cardiac toxicity.

The HERceptin Adjuvant (HERA) trial demonstrated that 1 year of trastuzumab following completion of anthracycline-based chemotherapy yielded comparable reductions in risk of recurrence (46%) and lower levels of cardiac toxicity. Patients with cardiac problems after chemotherapy were excluded from the study results.[53]

Recently, the BCIRG 006 trial included a non–anthracycline-containing regimen, TCH (docetaxel, carboplatin, trastuzumab). Although this regimen appeared comparably effective to AC followed by docetaxel plus trastuzumab (AC-DH), the relative reduction in risk from TCH compared to AC-DH was approximately 33%, raising the question of whether this cross-trial difference (vs 52% with AC-TH compared to AC-T in N9831/B-31) is due to a superior standard chemotherapy backbone, a less effective trastuzumab combination, or mere statistical chance.[54] For lymph node-negative patients, who were essentially not represented in B-31/N9831, this author typically uses TCH, but for young women with multinode-positive disease, I continue to use an N9831-style regimen. Other approaches are clearly acceptable, pending further data.

The lower limits of tumor size that benefit from trastuzumab are unclear, with most studies requiring tumors of 1 cm or greater for enrollment, and comparable reductions in relative risk of recurrence seen across all tumor sizes. Given that biology appears to trump size with regard to both recurrence risk and benefit from therapy, there is controversy over whether to treat tumors less than 0.5 cm (T1a) with adjuvant systemic therapy.[55] For HER2-positive patients, we would like to have data on trastuzumab alone, in combination with endocrine therapy, and with minimal chemotherapy. Clinical trials are underway to address each of these strategies.

Neoadjuvant vs Adjuvant Therapy

The discussion above has focused on adjuvant systemic therapy. Many young women with breast cancer will be candidates for neoadjuvant therapy, ie, systemic therapy preceding surgery. Overall, the large randomized clinical trials comparing adjuvant to neoadjuvant chemotherapy demonstrated no difference in disease outcomes. However, these investigations did show an increased likelihood
that patients with locally advanced breast cancer undergoing neoadjuvant therapy would have the option of breast-conserving surgery, compared to those undergoing adjuvant chemotherapy.[56] In addition to the increased chance for breast conservation, neoadjuvant therapy offers an opportunity to determine in a therapy is effective during treatment and a change to alternatives when indicated. This setting also offers an excellent opportunity for patients to consider clinical trials that can efficiently test new strategies and evaluate correlates of response and resistance to therapy. For patients who fail to achieve a pathologic complete response to neoadjuvant chemotherapy, clinical trials are underway to determine if additional chemotherapy combined with targeted strategies can reduce the risk of recurrence.[57]

**Fertility Concerns**

Concerns over fertility and desire for future pregnancy should be assessed in every patient under 40 considered for systemic therapy for breast cancer. Both endocrine therapy and chemotherapy have implications for the timing of any future pregnancy and fertility. Partridge et al have demonstrated that this is a major concern for young women with breast cancer, but the issue is not consistently addressed by oncologists.[58] Evidence suggests that most women under 40 will retain or recover their fertility after systemic chemotherapy, but long-term data on modern regimens are lacking.[17]

### REFERENCE GUIDE

**Therapeutic Agents**

- Carboplatin
- Clodronate
- Cyclophosphamide
- Docetaxel (Taxotere)
- Doxorubicin
- Epirubicin (Ellence)
- Fluorouracil (5-FU)
- Granulocyte colony-stimulating factor (G-CSF, Neupogen)
To date, studies with LHRH agonists to preserve fertility through ovarian suppression during chemotherapy have proven disappointing. Women can choose to undergo oocyte or embryo cryopreservation using AI-based protocols that appear safer than traditional in vitro fertilization techniques. However, data on successful pregnancies and long-term safety in this area are scant. Consideration of these issues requires referral to a reproductive specialist with experience in caring for young women with breast cancer. Fortunately, pregnancy following completion of breast cancer therapy appears to be safe.

**Summary**

The care of young women with breast cancer requires an understanding of the relatively higher risk for recurrence faced by this patient population and the range of options and issues that must be considered. While systemic therapy will still be guided primarily by breast cancer subtype as defined by endocrine receptor status and HER2, within each subcategory of disease multiple choices need to be considered, and for many questions data are emerging or nonexistent. In this context, it is important to at minimum deliver standard quality care with adjuvant tamoxifen for endocrine receptor–positive patients, chemotherapy for triple-negative patients, and a trastuzumab-based chemotherapy regimen for HER2- positive patients (with or without tamoxifen, depending on endocrine receptor status).

**Financial Disclosure:** Dr. Peppercorn has received honoraria for speaking (Genentech).

**Acknowledgment:** Dr. Peppercorn is supported by the American Society of Clinical Oncology and the Breast Cancer Research Foundation.
References:
negative axillary lymph node positive early breast cancer (abstract 77). San Antonio Breast Cancer Symposium; San Antonio, Tex; Dec 10-14, 2008.

Source URL: http://www.cancernetwork.com/oncology-journal/breast-cancer-women-under-40

Links:
[1] http://www.cancernetwork.com/review-article
[2] http://www.cancernetwork.com/oncology-journal
[4] http://www.cancernetwork.com/authors/jeffrey-peppercorn-md-mph