Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer

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INTRODUCTION

While fewer than one-third of women with newly diagnosed breast cancer are premenopausal [1], the choice of adjuvant endocrine therapy for hormone receptor-positive cancers is an important consideration regardless of menopausal status, particularly given the possibility of late recurrence with this subtype of breast cancer.

Tamoxifen has long been used in premenopausal women. Aromatase inhibitors (AIs) are not used as a single agent for those with intact ovarian function, though they may be combined effectively with ovarian function suppression (OFS) or ablation for appropriate candidates. Here we will discuss the choice of endocrine therapy for premenopausal women, for whom to use OFS or ablation, as well as selection of appropriate antiestrogen therapy.

The general approach to adjuvant endocrine therapy, including for postmenopausal women, is discussed elsewhere, as is the decision regarding whether to use chemotherapy (regardless of menopausal status). (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer" and "Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer", section on 'Special populations' and "Adjuvant systemic therapy for HER2-positive breast cancer", section on 'Patient eligibility' and "Deciding when to use adjuvant chemotherapy for hormone receptor-positive, HER2-negative breast cancer" and "Adjuvant systemic therapy for HER2-positive breast cancer".)

DEFINITION OF MENOPAUSE

Because the endocrine options for treatment depend on whether or not a woman is in menopause, defining menopausal status is important. We agree with the definition of menopause used by the National Comprehensive Cancer Network, which is discussed elsewhere. (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'Definition of menopause'.)

All women who do not meet the definition of menopause should be treated as premenopausal patients. For these patients, we base decisions regarding type of adjuvant endocrine therapy on the patient's risk of recurrence.

HIGHER-RISK, HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE CANCERS

Identification of higher-risk patients and approach — The addition of ovarian function suppression (OFS)/ablation to either an aromatase inhibitor (AI) or tamoxifen for some patients results in a clinically significant reduction in the risk of recurrence but does increase toxicity. As such, for those at higher risk for recurrence, we suggest OFS with an AI (or OFS with tamoxifen, as an alternative), given that this subset of patients has the highest likelihood of experiencing benefit. This recommendation is based on the results of the Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT), both of which are discussed below.

While formal criteria to define higher risk are not present, a reasonable definition would include patients with **either** of the following attributes:

- **Patients in whom chemotherapy is indicated** – Such as patients with the presence of pathologically involved lymph nodes, large tumor size, high risk of recurrence based on a genomic assay, or other high-risk features for which the patient received chemotherapy (algorithm 1). (See "Deciding when to use adjuvant chemotherapy for hormone receptor-positive, HER2-negative breast cancer".)

- **Patients at a younger age (ie, ≤35 years)** – We consider patients in this age group to be at a higher risk of recurrence, and hence we offer such women OFS, in addition to chemotherapy.

For patients not tolerating OFS, the option of tamoxifen alone followed by an AI after several years may be appropriate, depending on patient preferences, cancer risk factors, and the

timing of the transition to menopause. (See 'Transitioning from tamoxifen to an AI after menopause' below.)

Women who tolerate OFS without difficulty, plan to receive ongoing OFS, and are not interested in further childbearing or recovery of ovarian function in the future may consider surgical oophorectomy as an appropriate alternative to ongoing gonadotropin-releasing hormone agonist (GnRHa) treatment.

Ovarian suppression plus endocrine therapy

Methods of suppression — Ovarian function can be suppressed with a GnRHa or by permanent methods, such as oophorectomy or, rarely, irradiation. Any of these strategies is appropriate, depending on patient preferences, although we often start with a GnRHa and proceed to oophorectomy if OFS is tolerated.

- Appropriate GnRHas include goserelin, leuprolide, or triptorelin. We typically use the monthly rather than every-three-month formulations, as this was the dosing schedule used in the SOFT/TEXT trials discussed below. (See 'Efficacy in high-risk disease' below.)

Nevertheless, frequency of visits and access to treatment facilities must be considered. (See "COVID-19: Considerations in patients with cancer", section on 'Cancer treatment in uninfected patients'.)

- Oophorectomy results in reliable and prompt reduction in the levels of circulating estrogens but carries the risks associated with anesthesia and surgery [2]. The technical aspects of oophorectomy are covered elsewhere. (See "Oophorectomy and ovarian cystectomy".)

- Ovarian irradiation can be used to ablate ovarian function, although the limited data available suggest it may be more effective in women less than 40 years [3]. This requires cumulative doses over 12 Gy, as lower doses are associated with decreased efficacy. Because of the side effects of radiotherapy, this approach is rarely used in contemporary practice.

Efficacy in high-risk disease — As discussed above, we utilize OFS and either tamoxifen or an AI for high-risk, hormone receptor-positive patients.

The approach to OFS in premenopausal women is informed, in large part, by two large phase III trials of premenopausal women with operable, hormone receptor-positive breast cancer, in which use of chemotherapy was optional [4-8].

- In **SOFT**, over 3000 such women were randomly assigned to one of three arms: tamoxifen alone, tamoxifen plus OFS, or exemestane plus OFS [4]. Women were allowed to enter following surgery alone (in which case they were randomized within 12 weeks of surgery) or within eight months of the end of chemotherapy, provided they had biochemical proof they remained premenopausal.

- In **TEXT**, over 2600 premenopausal women were randomly assigned to receive tamoxifen plus OFS or exemestane plus OFS after surgery. In contrast to the SOFT trial, in TEXT, if chemotherapy was administered, OFS was initiated concurrently with chemotherapy.

Rationale for OFS — Subgroup analyses from the TEXT and SOFT trials suggest that patients with a higher risk of relapse derive a benefit with ovarian function suppression (OFS) plus either AI or tamoxifen versus tamoxifen alone [4,7-12]. Rationale for use of an AI over tamoxifen, when either is used in combination with OFS, is discussed below. (See 'Rationale for AI over tamoxifen, in combination with OFS' below.)

At twelve years, the following results were observed among premenopausal patients in the SOFT trial, 85 percent of whom had HER2 negative disease, and approximately half of whom had received chemotherapy in the (neo)adjuvant setting [12].

- In the intention to treat analysis, which included 3047 women:

  - Disease-free survival (DFS) – Tamoxifen alone had a lower DFS rate (72 percent) relative to both tamoxifen plus OFS (76 percent, HR 0.82) and exemestane plus OFS (79 percent, HR 0.69).

  - Overall survival (OS) – Tamoxifen alone resulted in a nonstatistically significant lower OS rate (87 percent) relative to tamoxifen plus OFS (89 percent, HR 0.86) and exemestane plus OFS (89.4 percent, HR 0.70).

- In the subgroup of patients with HER2-negative tumors, OS rates were 88 percent with tamoxifen, 89 percent with tamoxifen plus OFS, and 91 percent with exemestane plus OFS.

  - Among patients with HER2-negative disease and prior chemotherapy, OS rates were 79 percent with tamoxifen, 81 percent with tamoxifen plus OFS, and 84 percent with exemestane plus OFS. These differences did not reach statistical significance.

The benefits of OFS appear most pronounced in younger women (less than 35 years) as compared with women 35 years or older. In the SOFT trial, among 233 women younger than 35 years, the rate of freedom from breast cancer at five years was lower for patients treated with tamoxifen alone (68 percent) compared with those assigned to tamoxifen plus OFS and those

assigned to exemestane plus OFS (79 and 83 percent, respectively) [4]. Most, 94 percent, of these patients had also received chemotherapy.

Other trials have shown improvements in recurrence risk and modest improvements in OS with the addition of a GNRHa in premenopausal women receiving adjuvant chemotherapy.

- In the 2007 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis including over 2700 premenopausal women with hormone receptor-positive breast cancer treated with adjuvant chemotherapy (either with or without tamoxifen), the addition of a GnRHa reduced the risk of recurrence (HR 0.88, 95% CI 77.4-99.7) and hazard rate for death from recurrence (HR 0.85, 95% CI 72.4-99.9) [5].

- Additionally, in a trial of 1483 women with estrogen receptor-positive breast cancer treated with surgery and chemotherapy who remained premenopausal after treatment, the eight-year DFS for tamoxifen and OFS was 85 versus 80 percent for those receiving tamoxifen only (HR 0.67, 95% CI 0.51-0.87) [13]. There were no statistically significant differences in OS between the two groups (96.5 versus 95.3 percent respectively; HR 0.78, 95% CI 0.49-1.25) [14]. The length of OFS in this trial, two years, was shorter than in SOFT/TEXT, in which it was administered for five years. (See 'Duration of endocrine therapy' below.)

While other studies, including a randomized trial and a meta-analysis, have suggested similar DFS outcomes among patients (with either hormone receptor-positive or negative disease) receiving chemotherapy with or without a GnRHa, these studies were either underpowered to identify a beneficial DFS effect if it existed or were heterogeneous in regards to their patient populations [15,16].

Given the available data, we utilize OFS with endocrine therapy for high-risk, hormone receptor-positive premenopausal patients. (See 'Identification of higher-risk patients and approach' above.)

Rationale for AI over tamoxifen, in combination with OFS — Our preference is for an aromatase inhibitor (AI) rather than tamoxifen when combining with ovarian function suppression (OFS) for patients with high-risk disease.

A joint analysis of the SOFT-TEXT trials evaluated outcomes in 4690 premenopausal patients randomly assigned to 5 years of exemestane plus OFS versus tamoxifen plus OFS, with a median follow up of 13 years. Among patients with HER2-negative tumors (86 percent), exemestane plus OFS improved 12-year OS compared with tamoxifen plus OFS by 2 percent (91 versus 89 percent, HR 0.85; 95% CI, 0.70 to 1.04), with a 3.3 percent absolute benefit among

those who received chemotherapy [17]. In subset analyses, which did not achieve statistical significance, the magnitude of benefit was greatest in high-risk patients (eg, women aged <35 years [4.0 percent] and those with >2 cm [4.5 percent] or grade 3 tumors [5.5 percent]).

Similar findings were described in a meta-analysis by the EBCTCG that included the ABCSG-12 and HOBOE trials in addition to SOFT and TEXT [18]. Among over 7000 patients with hormone receptor-positive breast cancer receiving adjuvant OFS, 40 percent of whom were node positive, 10-year recurrence rates were 18 percent with tamoxifen and 15 percent with an AI (relative risk [RR] 0.79, 95% CI 0.69-0.90). These benefits were primarily observed in years 0 through 4, when treatments differed, but were not observed in years 5 and beyond. Distant recurrences were also improved with AI administration (absolute improvement at 10 years of 1.9 percent; RR 0.83, 95% CI 0.71-0.97), although breast cancer mortality rates were similar (RR 1.01).

Toxicity — Side effects related to tamoxifen and AIs, and their management, are discussed elsewhere. (See "Managing the side effects of tamoxifen and aromatase inhibitors".)

The side effect profile of OFS or ablation mimics symptoms of estrogen deprivation, as with menopause. These include hot flashes, sweats, weight gain, and decreased libido. (See "Clinical manifestations and diagnosis of menopause", section on 'Clinical manifestations'.)

- Toxicities with OFS with GnRHas include musculoskeletal symptoms, hot flashes, and bone mineral density loss.
    - Across both SOFT and TEXT, toxicities were greater among those receiving OFS relative to single-agent tamoxifen. Of the women receiving OFS, those treated with exemestane versus tamoxifen experienced more osteoporosis and musculoskeletal complaints, though overall severe toxicities were similar, as follows [7,9]:
        - Osteoporosis in 42 percent with exemestane plus OFS, 28 percent with tamoxifen plus OFS, and 14 percent with tamoxifen only, respectively.
        - Musculoskeletal symptoms in 90 percent with exemestane plus OFS, 78 percent with tamoxifen plus OFS, and 70 percent with tamoxifen only, respectively.
        - Grade 3 or 4 adverse events in 32 percent with exemestane plus OFS, 31 percent with tamoxifen plus OFS, and 25 percent with tamoxifen only, respectively.

          A separate study also suggested that the combination of OFS and tamoxifen resulted in worse menopausal symptoms and a higher incidence of sexual dysfunction relative to tamoxifen alone, resulting in a lower health-related quality of life at three years [6].

- For women who undergo either oophorectomy or ovarian ablation, premature menopause may be associated with long-term health effects, including cardiovascular disease. (See "Overview of atherosclerotic cardiovascular risk factors in females", section on 'Early menopause'.)

- For women undergoing ovarian irradiation, despite tailoring the treatment field to the ovaries, there is a risk of radiation to the normal tissue surrounding the ovary, including the bowels. (See "Overview of gastrointestinal toxicity of radiation therapy".)

Sequencing ovarian suppression with other systemic therapies — Although some UpToDate experts prefer to start a GnRHa after chemotherapy and add AIs two to three months later, given the possibility of a delay in OFS, others initiate OFS and AIs in tandem, according to the SOFT/TEXT trials discussed above [4-8]. For those who will be treated with tamoxifen and OFS, they are initiated concurrently.

Addition of targeted therapies for select, high-risk cancers

Addition of CDK 4/6 inhibitor to adjuvant endocrine therapy in high-risk disease — Abemaciclib is approved by the US Food and Drug Administration as adjuvant therapy for **select** women with high-risk, node-positive hormone receptor-positive, HER2-negative breast cancer [19]. Selection of patients for this therapy is the same regardless of menopausal status, and is discussed elsewhere. (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'CDK 4/6 inhibitors for select patients with high risk disease'.)

In the monarchE trial, over 5600 patients (just under one-half of whom were premenopausal women) with hormone receptor-positive, HER2-negative, high-risk early breast cancer who had completed surgery were randomly assigned to abemaciclib with endocrine therapy or endocrine therapy alone [20]. At a median of 19 months' follow-up, in the premenopausal subset, adjuvant abemaciclib plus endocrine therapy improved both invasive DFS (HR 0.63, 95% CI 0.44-0.92) and distant relapse-free survival (HR 0.71, 95% CI 0.56-0.92) relative to adjuvant endocrine therapy alone [20]. Results at longer follow-up of 27 months were consistent [21]. The most frequent adverse events were diarrhea, neutropenia, and fatigue in the abemaciclib arm and arthralgia, hot flush, and fatigue in the control arm.

Further details and results of this and other relevant trials are discussed elsewhere, given that they included both pre- and postmenopausal patients. (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'Incorporation of targeted therapies for select patients'.)

Olaparib for select high risk, BRCA-mutated cancers — The use of adjuvant olaparib in *BRCA*-carriers with HER2-negative, high-risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy is discussed in detail elsewhere. (See "Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer".)

LOW- TO AVERAGE-RISK, HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE CANCERS

Preference for tamoxifen — For most women who appear not to be at high risk of recurrence, and who are over the age of 35 years, we initiate tamoxifen as single-agent therapy (algorithm 1). However, some women at average risk of relapse, particularly those who have residual breast tissue and are therefore at risk for a new breast primary, may reasonably choose to pursue ovarian function suppression (OFS) in addition to an aromatase inhibitor (AI) if they prioritize minimizing the risk of relapse over potential side effects and toxicities. (See 'Ovarian suppression plus endocrine therapy' above.)

For many women who initiate single-agent tamoxifen, we transition to an AI later in the course of therapy if the patient remains amenorrheic and has follicle-stimulating hormone (FSH) and serum estradiol levels that are in the postmenopausal range. (See 'Patients who became amenorrheic during chemotherapy' below.)

The data regarding tamoxifen in randomized trials are discussed below, according to the comparator:

Tamoxifen versus OFS plus endocrine therapy — The use of ovarian function suppression (OFS) with either tamoxifen or AI provides some benefit in terms of disease-free survival (DFS) over tamoxifen alone, but also is associated with increased toxicity [7].

For the 46 percent of women participating in the Suppression of Ovarian Function Trial (SOFT) who did not receive chemotherapy (ie, patients at average or lower risk for recurrence), there was no improvement in distant recurrences (over 97 percent of patients free of distant recurrences in all groups) or in overall survival (OS). A modest improvement in freedom from breast cancer at eight years was found in those receiving OFS and exemestane versus tamoxifen alone (95 versus 91 percent with tamoxifen alone; hazard ratio [HR] 0.59, 95% CI 0.35-0.98), but no statistical improvement with OFS and tamoxifen over tamoxifen alone (DFS 94 versus 91 percent; HR 0.83, 95% CI 0.52-1.32) was found.

By contrast, in a 2007 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, the addition of a gonadotropin-releasing hormone agonist (GnRHa) to tamoxifen did not

improve recurrences (HR 0.85, 95% CI 0.67-1.09) [5]. A possible reason for this difference was the smaller number of patients in the meta-analysis versus in the SOFT trial receiving tamoxifen alone (approximately one-half as many), making a statistically significant difference more difficult to detect. In addition, prior to the SOFT/TEXT studies, many women included in trials of GnRHa therapy also received chemotherapy, which rendered them menopausal, and rendered the trials markedly confounded.

Importantly, in preliminary reporting of SOFT at longer follow-up (median 12 years), among patients not receiving chemotherapy, OFS with either tamoxifen or an AI did not improve distant recurrences or OS relative to tamoxifen alone [22]. Over 95 percent of patients in all groups survived without distant recurrences.

Taken together, these data suggest a possible modest DFS benefit with the addition of OFS to an AI over tamoxifen alone for patients with hormone receptor-positive breast cancer, but given the lack of benefit in DFS or OS, in the author's opinion does not justify the more intensive side effects for most average-risk patients. (See 'Low- to average-risk, hormone receptor-positive, HER2-negative cancers' above.)

Tamoxifen versus placebo — The rationale for tamoxifen versus placebo comes from a 2011 EBCTCG meta-analysis including trials of both post- and premenopausal women, in which five years of tamoxifen improved both breast cancer recurrences and mortality by 30 to 40 percent [23]. These data are discussed in detail elsewhere. (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'Efficacy of tamoxifen versus placebo'.)

A separate randomized trial has shown that even at 20 years of follow-up there are durable benefits to two years of adjuvant tamoxifen treatment in premenopausal patients [24].

Toxicities of tamoxifen are discussed in detail elsewhere. (See "Managing the side effects of tamoxifen and aromatase inhibitors".)

Transitioning from tamoxifen to an AI after menopause — For many women who are premenopausal at diagnosis and initiate treatment with tamoxifen, we transition to an aromatase inhibitor (AI) after several years of treatment if clinical and biochemical evidence of menopause is apparent. Clinical monitoring of menses is insufficient given that women may be amenorrheic and still have biochemical recovery of ovarian function, leading to worse disease outcomes on AIs. Therefore, we assess FSH and serum estradiol prior to making the transition and for several months after transitioning to AIs to ensure that these women do not have ovarian function reactivation.

Toxicities of AIs are discussed elsewhere. (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'Side effects'.)

Risk of ovarian function reactivation on an AI — Recovery of ovarian function with aromatase inhibitors (AIs) has a negative effect on breast cancer outcomes.

For example, a study of approximately 50 women transitioned from tamoxifen to exemestane after two years of chemotherapy-induced amenorrhea and postmenopausal E2 levels suggested that women recovering ovarian function (as demonstrated either by resumption of menses or by biochemical recovery of function) on exemestane experienced a lower rate of DFS at two years compared with those who did not (82 versus 100 percent; HR for recurrence 9.3, 95% CI 3.3-48.0) [25]. Although this is a relatively small study, it demonstrates the risks of using AIs in women with chemotherapy-induced amenorrhea.

The risk of recovering ovarian function with AI treatment alone appears to be age related, although it has been observed even in women in their early 50s. In one study, 173 women aged 40 to 49 years who had estrogen receptor-positive breast cancer, chemotherapy-induced amenorrhea, and postmenopausal serum estrogen levels after chemotherapy were transitioned to letrozole after a median of 19 months of tamoxifen treatment. Of these patients, 6 percent resumed menses and 32 percent developed premenopausal serum estradiol levels (without menses) at a median time of 8.8 months after initiation of AI [26].

Additionally, some women on OFS and AIs do not achieve consistently low estradiol levels. In a prospective substudy of SOFT, the SOFT Estrogen Suppression Study (SOFT-EST), estradiol levels were measured in a central laboratory at several time points during the first year of therapy with triptorelin, and, at each time point, 17 percent of the women receiving OFS and exemestane were found to have levels above those that have been reported in postmenopausal women on AIs [27]. The clinical relevance of this finding is unknown, however, as we do not know if estradiol levels predict the benefit of OFS and AI.

HORMONE RECEPTOR-POSITIVE, HER2-POSITIVE CANCERS

Most patients with HER2-positive cancers will receive chemotherapy, either in the neoadjuvant or adjuvant setting; however, there are few data to inform the benefit of ovarian function suppression (OFS) among patients with HER2-positive cancers, as these patients represented a small minority (approximately 12 percent) in the SOFT trial [4], and only about 60 percent

received HER2-targeted therapy, which would be standard of care according to current treatment guidelines.

Recognizing the limitations in available data, our approach to premenopausal patients with hormone receptor-positive, HER2-positive disease is as follows:

- For those who receive neoadjuvant therapy and have residual disease, we suggest the addition of OFS with endocrine therapy in the adjuvant setting.
- For those who receive neoadjuvant therapy and have a pathologic complete response, either use of OFS or omission of OFS are acceptable, depending on patient preference, as there are no data to inform this choice. Some patients may elect for OFS, extrapolating from benefits in the metastatic setting and also from HER2-negative disease. However, others may feel that the lack of proven benefit and the known added toxicity do not justify pursuing OFS.
- For those who had small (<2 cm), node negative cancers, chemotherapy is typically administered in the adjuvant rather than neoadjuvant setting. For these patients, we suggest tamoxifen alone rather than OFS plus endocrine therapy.

DURATION OF ENDOCRINE THERAPY

The minimum duration of treatment with endocrine therapy is five years, although extended treatment to 10 years is appropriate in women with higher-risk disease. For women with smaller, node-negative tumors, such as those who are candidates for tamoxifen alone, it is not clear that there is a sufficiently high risk of late recurrence to justify the side effects and risks of extended endocrine therapy, and a decision should be made based on individual preferences. Women who are tolerating endocrine treatment well and place a high value on minimizing their risk of new breast cancers may reasonably choose extended endocrine therapy, whereas women who place a higher value on avoidance of side effects may reasonably choose to stop endocrine therapy after five years.

The approach to duration of endocrine therapy in premenopausal women is extrapolated from trials that enrolled either exclusively or mostly postmenopausal women. Full discussion, including patient selection for extended treatment, efficacy, and toxicities, is covered elsewhere. (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'Duration of endocrine treatment'.)

Menopausal status cannot be assessed in women receiving gonadotropin-releasing hormone agonists (GnRHa) who are amenorrheic. As such, for premenopausal women receiving ovarian function suppression (OFS) with a GnRHa, we continue it for the duration of endocrine therapy or offer oophorectomy, if OFS is well tolerated. One trial has evaluated a shorter course of OFS (two years) [13], with promising results, but two versus five years have not been compared in a head-to-head fashion, and we would therefore stop at two years only for those not tolerating treatment.

SPECIAL CONSIDERATIONS

Patients who became amenorrheic during chemotherapy — For women with breast cancer who were premenopausal at diagnosis, particularly those treated with adjuvant chemotherapy, amenorrhea is not a reliable indicator of menstrual status. Such women may recover ovarian function. There are no tests that can reliably predict whether or when ovarian function might occur (though chemotherapy-induced menopause is more likely to be permanent in patients in their mid-40s and above). For that reason, premenopausal women with chemotherapy-induced amenorrhea should be treated as premenopausal. For such women, if an aromatase inhibitor (AI) is being considered after completion of chemotherapy, it should only be used in conjunction with either gonadotropin-releasing hormone agonist (GnRHa) therapy or following oophorectomy [25,26,28]. (See 'Ovarian suppression plus endocrine therapy' above.)

For women with average-to-low-risk cancers, tamoxifen alone may be initiated, and a transition to an AI alone after several years may be appropriate when clinical and biochemical evidence of menopause is apparent. (See 'Transitioning from tamoxifen to an AI after menopause' above.)

Importance of contraception — Women who are of childbearing potential can remain fertile on tamoxifen and should be advised to use an effective means of contraception while on tamoxifen treatment (we consider ovarian function suppression adequate for contraception, for those who are additionally receiving this therapy and are compliant). (See "Approach to the patient following treatment for breast cancer", section on 'Contraception after breast cancer'.)

Following completion of tamoxifen treatment, a waiting period of **two months** from drug discontinuation prior to attempting pregnancy is suggested to ensure that it has been cleared from the body [29].

For women who become pregnant while taking tamoxifen, tamoxifen should be discontinued because its use during pregnancy is associated with congenital anomalies. As an example, one study, which evaluated the frequency of birth defects associated with tamoxifen through a

literature review and access to the records from the drug manufacturer of tamoxifen, reported [29]:

- Of seven live births from women who took tamoxifen before pregnancy, three babies (43 percent) were born with a congenital anomaly.
- Of 138 live births from women who took tamoxifen during pregnancy, 16 (12 percent) were born with a congenital malformation. By comparison, the baseline rate of congenital malformations is 3 to 4 percent.

The management of women diagnosed with breast cancer during pregnancy is discussed separately. (See "Gestational breast cancer: Treatment", section on 'Endocrine therapy'.)

Fertility preservation — Details regarding the use of GnRHa for fertility preservation during chemotherapy are discussed elsewhere [30,31]. (See "Fertility and reproductive hormone preservation: Overview of care prior to gonadotoxic therapy or surgery".)

APPROACHES NOT USED

Historically, in an era before widespread use of adjuvant endocrine therapy with tamoxifen or an aromatase inhibitor, ovarian function suppression as a single-modality treatment was utilized. However, it is not commonly used alone in contemporary practice for patients with early-stage breast cancer given the benefits that have been observed with other endocrine therapies.

In the 2007 Early Breast Cancer Trialists' Collaborative Group meta-analysis discussed above, a gonadotropin-releasing hormone agonist used as a single agent resulted in a nonsignificant trend toward a lower risk of breast cancer recurrence compared with no other types of systemic treatment (hazard ratio [HR] 0.72, 95% CI 0.49-1.04). There was also a nonsignificant trend toward a reduction in mortality (HR 0.82, 95% CI 0.47-1.43), though the analysis was likely underpowered for this outcome [32].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Breast cancer".)

SUMMARY AND RECOMMENDATIONS

- **Introduction and treatment algorithm** – Approximately one-third of women with newly diagnosed breast cancer are premenopausal. For those with hormone receptor-positive cancers, the approach to choosing an endocrine agent is an important consideration, which differs relative to that in postmenopausal women. (See 'Introduction' above.)

  Our initial treatment approach to premenopausal women with non-metastatic, hormone receptor-positive, HER2-negative breast cancer is summarized in the algorithm (algorithm 1).

- **Hormone receptor-positive, HER2-negative cancers**

  While formal criteria to define higher risk are not present, we define this subgroup as patients in whom chemotherapy is indicated (eg, patients with the presence of pathologically involved lymph nodes, large tumor size, high risk of recurrence based on a genomic assay, or other high-risk features for which the patient received chemotherapy). (See "Deciding when to use adjuvant chemotherapy for hormone receptor-positive, HER2-negative breast cancer".)

  In addition, we also consider women at a younger age (ie, ≤35 years) to be at a higher risk of recurrence. (See 'Identification of higher-risk patients and approach' above.)

  - **Higher-risk patients** – For women with high-risk, hormone receptor-positive breast cancer, we suggest incorporation of ovarian function suppression (OFS) plus an aromatase inhibitor (AI) or tamoxifen, rather than tamoxifen alone (**Grade 2B**). When using OFS, we suggest use of an AI rather than tamoxifen (**Grade 2C**).

    Incorporation of abemaciclib is an appropriate option for select patients with high-risk, node-positive hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer, irrespective of menopausal status, and is discussed in detail elsewhere. (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'CDK 4/6 inhibitors for select patients with high risk disease'.)

  - **Average or low-risk patients** – For women with average-low-risk breast cancer, we suggest tamoxifen as single-agent therapy rather than OFS plus endocrine therapy (**Grade 2C**). The rationale for this recommendation is the better tolerability than OFS plus either an AI or tamoxifen. We typically consider low-risk breast cancer to be in women older than 35 years who are without indications for chemotherapy. However, some women who prioritize minimizing the risk of recurrence over side effects may

reasonably opt for OFS plus an AI or tamoxifen. (See 'Low- to average-risk, hormone receptor-positive, HER2-negative cancers' above.)

Single-agent use of an AI as cancer therapy in women with intact ovarian function is contraindicated. In women who were premenopausal at diagnosis and became amenorrheic during the course of chemotherapy, AIs are initiated only with concurrent OFS or ablation.

- **Hormone receptor-positive, HER2-positive cancers** – There are few data to inform the approach in this subset. Recognizing that other approaches are acceptable, given the limitations in data, our approach is as follows:

  - For such patients with residual disease after neoadjuvant therapy, we suggest incorporation of OFS with endocrine therapy in the adjuvant setting (**Grade 2C**). For those with a pathologic complete response after neoadjuvant therapy, either use of OFS or omission of OFS is appropriate, depending on patient preference.

  - For patients with small (<2 cm), node-negative cancers, chemotherapy is typically administered in the adjuvant rather than neoadjuvant setting. For such patients, we typically suggest tamoxifen alone rather than OFS plus endocrine therapy (**Grade 2C**).

- **Duration of treatment** – The minimum duration of treatment with endocrine therapy is five years, although extended treatment to 10 years is appropriate in women with higher-risk disease as well as some women with lower-risk disease who prefer to minimize the risks of recurrence, despite increased toxicities. The approach to duration of endocrine therapy in premenopausal women is extrapolated from the postmenopausal setting. Full discussion, including patient selection, efficacy, and toxicities, is covered separately. (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'Duration of endocrine treatment'.)

- **Toxicities**

  - Toxicities with OFS with gonadotropin-releasing hormone agonists include musculoskeletal symptoms, hot flashes, and bone mineral density loss. Combination of OFS with either tamoxifen or an AI results in typically greater toxicity than tamoxifen alone. (See 'Toxicity' above and "Managing the side effects of tamoxifen and aromatase inhibitors".)

  - There is a high frequency of congenital anomalies associated with tamoxifen if taken during pregnancy. Women who are of childbearing potential should use an effective

means of contraception while on tamoxifen. Those who become pregnant while on tamoxifen should discontinue it during pregnancy. Following completion of tamoxifen treatment, given the pharmacokinetics of the drug, women are advised to wait for at least two months after tamoxifen has been discontinued before attempting pregnancy. (See 'Importance of contraception' above.)

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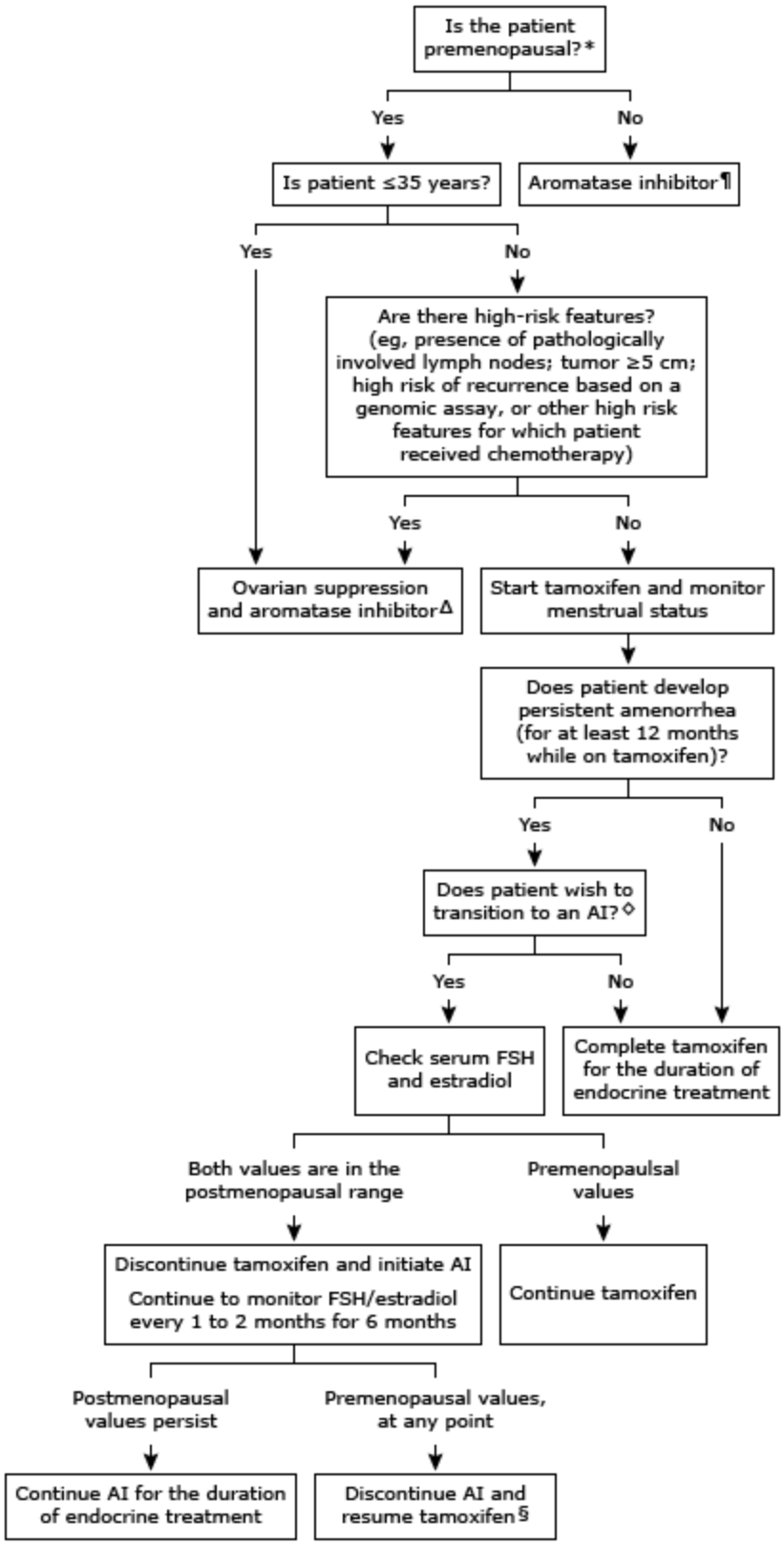
GRAPHICS

Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer



- For women receiving adjuvant endocrine therapy, we recommend at least a five-year course of treatment. If there has been no disease recurrence at that point, our approach to extended endocrine treatment is as follows. For women with higher-risk disease (eg, ≥T3 or lymph node positive), we suggest an additional five years of endocrine treatment. Those who have been treated with tamoxifen only rather than an AI may have a higher likelihood of benefit.
- For women with smaller, node-negative tumors, it is not clear that there is a sufficiently high risk of late recurrence to justify the side effects and risks of extended endocrine therapy. Women who are tolerating endocrine treatment well and place a high value on minimizing their risk of new breast cancers may reasonably choose extended endocrine therapy, whereas women who place a higher value on avoidance of side effects may reasonably choose to stop endocrine therapy after five years.

AI: aromatase inhibitor; FSH: follicle-stimulating hormone; GnRHa: gonadotropin-releasing hormone agonist.

* For women with breast cancer who were premenopausal at diagnosis, particularly those treated with adjuvant chemotherapy, amenorrhea is not a reliable indicator of menstrual status. We agree with the following definitions of menopause used by the National Comprehensive Cancer Network:[1]

- Women 60 years and older are postmenopausal.
- Women less than 60 years are postmenopausal if one of the following conditions is met:
  - They previously underwent a bilateral oophorectomy.
  - They have not had any menstrual periods for 12 months or more in the absence of tamoxifen, chemotherapy, or ovarian suppression, and the serum estradiol is in the postmenopausal range.
  - They are amenorrheic on tamoxifen, and FSH and serum estradiol are in the postmenopausal range.

¶ For postmenopausal women with non-metastatic, hormone receptor-positive breast cancer, we suggest an AI rather than tamoxifen as adjuvant endocrine treatment. While AIs are associated with improved outcomes compared with tamoxifen, both agents reduce recurrences and new primary breast cancers, and some women may tolerate the risks and toxicities of tamoxifen better than an AI. For women who wish to discontinue an AI, it would be reasonable to switch to tamoxifen. Refer to UpToDate topic on adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive breast cancer.

Δ Although AIs with ovarian suppression (or ablation) are the preferred option for premenopausal women with breast cancer that has high-risk features, decisions regarding treatment are individualized based on patients' preferences, other health issues, and tolerance of therapy. Alternative options for select patients may include ovarian suppression with tamoxifen or tamoxifen alone. For those initiating ovarian suppression, we typically start with a GnRHa and continue it for the duration of endocrine therapy, or offer oophorectomy, if ovarian suppression has been well tolerated.

◇ In counseling patients regarding a possible transition to an AI, we discuss the modest improvements in efficacy with AIs over tamoxifen, as well as the respective side effect profiles. Decisions regarding treatment are individualized based on patients' preferences, anticipated remaining duration of therapy (both if continuing on tamoxifen or if transitioning to an AI), tolerance of therapy, and other health issues. Refer to UpToDate discussions on adjuvant endocrine therapy for hormone receptor-positive breast cancer.

§ Depending on duration of remaining treatment, one could reassess FSH and estradiol in 12 months, and consider a transition to an AI at that time, if values are in the postmenopausal range.

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Graphic 126073 Version 2.0

Contributor Disclosures

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