oncology grand rounds

Improving Adjuvant Endocrine Treatment Tailoring in Premenopausal Women With Hormone Receptor–Positive Breast Cancer

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The Oncology Grand Rounds series is designed to place original reports published in the Journal into clinical context. A case presentation is followed by a description of diagnostic and management challenges, a review of the relevant literature, and a summary of the authors' suggested management approaches. The goal of this series is to help readers better understand how to apply the results of key studies, including those published in Journal of Clinical Oncology, to patients seen in their own clinical practice.

INTRODUCTION

The Oncology Grand Rounds series is designed to place original reports published in the *Journal of Clinical Oncology* into clinical context. A case presentation is followed by a description of diagnostic and management challenges, a review of the relevant literature, and a summary of the authors' suggested management approaches. The goal of this series is to help readers better understand how to apply the results of key studies, including those published in *JCO*, to patients seen in their own clinical practice.

CASE PRESENTATIONS

A 41-year-old premenopausal woman was diagnosed with stage I breast cancer; she underwent lumpectomy and sentinel lymph node dissection for a left-sided breast cancer measuring 1.1 cm. None of the two sentinel lymph nodes contained metastatic carcinoma. The tumor had ductal histology and was considered grade 1 of 3. Immunohistochemical studies showed that the tumor was strongly positive for estrogen and progesterone receptor expression, was negative for human epidermal growth factor receptor 2 (HER2) overexpression, and had a Ki-67 score of 11%.

A 39-year-old premenopausal woman was diagnosed with stage I breast cancer; she underwent mastectomy and sentinel lymph node dissection for a right-sided breast cancer measuring 1.1 cm. The sentinel lymph node did not contain metastatic carcinoma. The tumor had ductal histology and was considered grade 2 of 3. Immunohistochemical analysis showed HER2-negative disease with intermediate positivity for estrogen and progesterone receptor expression. A 21-gene assay was requested and returned a recurrence score (RS) of 21.

A 40-year-old premenopausal woman presented with stage II breast cancer; she underwent quadrantectomy and sentinel lymph node dissection for a left-sided breast cancer measuring 1.1 cm. One of three sentinel lymph nodes contained metastatic carcinoma. The tumor had ductal histology and was considered grade 2 of 3. Immunohistochemical studies showed HER2-negative disease with intermediate positivity for estrogen and progesterone receptor expression. At another institution, adjuvant chemotherapy followed by radiation therapy (without axillary dissection) and endocrine therapy was recommended. After four cycles of adjuvant docetaxel and cyclophosphamide, she developed chemotherapy-induced amenorrhea; nevertheless, a blood test 1 month after chemotherapy completion showed estradiol and follicle-stimulating hormone (FSH) levels in the premenopausal range. She came to our attention seeking a second opinion to discuss the optimal adjuvant endocrine treatment.

A 39-year-old premenopausal woman was diagnosed with stage II breast cancer; she underwent mastectomy and axillary node dissection for a right-sided breast cancer measuring 2.3 cm. Three of twelve axillary nodes contained metastatic carcinoma. The tumor had ductal histology and was considered grade 3 of 3. Immunohistochemical analysis showed HER2-negative disease with high (95%) and intermediate (40%) positivity for estrogen and progesterone receptor expression, respectively.

All four clinical cases were discussed at our weekly multidisciplinary tumor board.

CHALLENGES IN DIAGNOSIS AND MANAGEMENT

Breast cancer is the most common malignancy in premenopausal women,[1] accounting for more than 50% of all new occurrences in some countries.[2] Despite higher chances of developing aggressive breast cancer subtypes, the majority of tumors in premenopausal patients have positive estrogen and progesterone receptor expression.[3] Therefore, endocrine treatment is a mainstay adjuvant therapy for these patients. Optimal and refined estimation of prognosis and treatment benefit are key factors for choosing the best adjuvant treatment, which includes

ASSOCIATED CONTENT

See accompanying article doi 10.1200/JCO.18.01967

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on September 13, 2019 and published at jco.org on October 16, 2019: DOI https://doi.org/10.1200/JCO.19.02242

the possibility of adding chemotherapy in women with hormone receptor–positive tumors.[4] This is of particular relevance for premenopausal patients, given the significant chemotherapy-related risk of long-term adverse effects with major impact on quality of life.[5] These potential age-related negative consequences of chemotherapy include impairment of fertility and chances of future motherhood, which are highly relevant concerns that influence patient choices and adherence toward the recommended treatments and subsequently their disease-related outcomes.[6-8]

Age and menopausal status are crucial factors in the choice of the optimal adjuvant treatment.[4] Recent data suggest that the known independent poor prognostic value of young age at diagnosis is restricted to hormone receptor–positive tumors.[9-11] There are possible clinical and biologic explanations for these findings. First, these studies were conducted when tamoxifen alone was considered the standard of care as adjuvant endocrine treatment.[12] Therefore, a significant proportion of premenopausal patients were undertreated according to current recommendations.[13] Second, young age is associated with suboptimal adherence to adjuvant endocrine treatment.[14,15] Fertility and pregnancy-related concerns represents key factors for noninitiation and early treatment discontinuation.[16,17] Finally, there are potential biologic differences between breast cancers arising in young and older patients,[18,19] particularly for hormone receptor–positive tumors.[20] These data further highlight that specific attention should be paid to the management—including selection of the best adjuvant endocrine treatment—of hormone receptor–positive breast cancer in premenopausal women.

For many years, tamoxifen has been the standard adjuvant endocrine treatment option for premenopausal women with hormone receptor–positive tumors.[12] In recent years, evidence on the role of ovarian function suppression (OFS) added to tamoxifen or to an aromatase inhibitor (AI) has radically changed the endocrine treatment landscape in this setting.[13] Although a better understanding about how to integrate genomic information with classic clinicopathologic features has significantly improved our ability to estimate patient prognosis and chemotherapy benefit,[21,22] adjuvant endocrine treatment tailoring in premenopausal women remains challenging.[23,24] Therefore, having a new tool that could aid and engage patients and physicians during endocrine treatment decision making represents an important resource with a crucial impact on daily clinical practice.

SUMMARY OF THE RELEVANT LITERATURE

Evolving Adjuvant Endocrine Treatment Landscape in Premenopausal Women

The use of tamoxifen for 5 years significantly reduces the risk of breast cancer recurrence and death during the first 15 years after diagnosis in all patients with hormone receptor–positive tumors, irrespective of age at diagnosis.[25] In premenopausal patients with hormone receptor–positive breast cancer, the development of chemotherapy-induced amenorrhea is associated with improved prognosis.[26,27] Nevertheless, the benefit of temporary (ie, using a gonadotropin-releasing hormone agonist [GnRHa]) or permanent (ie bilateral oophorectomy or ovarian irradiation) OFS in addition to tamoxifen has remained unclear until recently.[28] Three trials have now clarified the role of escalating adjuvant endocrine treatment by combining OFS with tamoxifen (Table 1).[29-31] The E-3193 INT-0142 study did not show any difference in disease-free survival (DFS) or overall survival (OS) between patients treated with tamoxifen alone or combined with OFS for 5 years.[29] Notably, this was a small trial that included low-risk patients (primary tumors $\leq$ 3 cm, node-negative disease, no prior adjuvant chemotherapy allowed). Conversely, a significant DFS and OS improvement was observed by adding OFS to tamoxifen in the updated analysis of SOFT and in the ASTRRA study.[30,31] SOFT was a three-arm trial in which premenopausal patients were randomly allocated to receive tamoxifen alone or combined with OFS or the combination of OFS plus exemestane.[32] OFS was administered for 5 years; patients with or without exposure to prior chemotherapy were included, but those who received cytotoxic therapy (53% of the study population) could be randomly assigned within 8 months after its completion only in the presence of premenopausal estradiol levels (and during this period, patients were allowed to receive tamoxifen alone). The survival benefits observed for the primary comparison (tamoxifen plus OFS *v* tamoxifen alone) were more evident in patients with prior exposure to chemotherapy and in women younger than age 35 years.[30] In the ASTRRA trial, OFS was administered for 2 years; only patients who received prior chemotherapy were eligible if they remained premenopausal or resumed ovarian function (defined by menstrual history or FSH levels) within 2 years after its completion.[33]

By providing the most profound suppression of hormone serum levels,[34,35] the combination of OFS plus an AI represents another step in escalating adjuvant endocrine treatment. Three trials assessed this combination (Table 2).[30,36,37] With a two-by-two factorial design, the ABCSG-12 study randomly allocated patients to receive OFS plus anastrozole or tamoxifen with or without zoledronic acid. Patients who received OFS plus anastrozole had similar DFS but worse OS compared with those who received OFS plus tamoxifen.[36] Notably, adjuvant endocrine treatment was administered for 3 years, half of the study population also received adjuvant bisphosphonates, and low-risk patients were included (75% with primary tumors $\leq$ 2 cm, 66% with node-negative disease, and only 5% with prior exposure to neoadjuvant chemotherapy [adjuvant cytotoxic therapy was not allowed]).[38] TEXT randomly allocated premenopausal patients with hormone receptor–positive tumors to 5 years of OFS plus tamoxifen or exemestane.[39] As in SOFT, patients were allowed to receive prior chemotherapy but, when administered (60%

TABLE 1. Main Results of the Trials Investigating the Combination of OFS and Tam

			DFS			OS		
Study	**No. of Patients***	**Follow-Up (years)**	**OFS + Tam (%)**	**Tam Alone (%)**	**HR (95% CI): OFS *v* None**	**OFS + Tam (%)**	**Tam Alone (%)**	**HR (95% CI): OFS *v* None**
Cuzick et al (meta-analysis)[28]	1,013	6.8	NR	NR	0.85 (0.67 to 1.09)	NR	NR	0.84 (0.59 to 1.19)
E-3193 INT-0142[29]	337	9.9	5-year: 89.7	5-year: 87.9	1.17† (0.64 to 2.12)	5-year: 97.6	5-year: 95.2	1.19† (0.52 to 2.70)
ASTRRA[31]	1,282	5.3	5-year: 91.1	5-year: 87.5	0.69 (0.48 to 0.97)	5-year: 99.4	5-year: 97.8	0.31 (0.10 to 0.94)
SOFT[30]‡	2,033	8.0	8-year: 83.2	8-year: 78.9	0.76 (0.62 to 0.93)	8-year: 93.3	8-year: 91.5	0.67 (0.48 to 0.92)

Abbreviations: DFS, disease-free survival; HR, hazard ratio; NR, not reported; OFS, ovarian function suppression; OS, overall survival; Tam, tamoxifen.
*Analyzed for efficacy.
‡Only the comparison between OFS + Tam *v* Tam alone is presented (the OFS + exemestane arm is not reported).
†Adjusted HR.

TABLE 2. Main Results of the Trials Investigating the Combination of OFS and an AI

			DFS			OS		
Study	**No. of Patients***	**Follow-Up (years)**	**OFS + AI (%)**	**OFS + Tam (%)**	**HR (95% CI): AI *v* Tam**	**With OFS + AI (%)**	**With OFS + Tam (%)**	**HR (95% CI): AI *v* Tam**
ABCSG-12[36]†	1,803	7.9	NR	NR	1.13 (0.88 to 1.45)	NR	NR	1.63 (1.05 to 2.52)
Joint analysis SOFT and TEXT[30]‡	4,690	9.0	8-year: 86.8	8-year: 82.8	0.77 (0.67 to 0.90)	8-year: 93.4	8-year: 93.3	0.98 (0.79 to 1.22)
HOBOE[37]§	710	5.3	5-year: 93.2	5-year: 85.4	0.72 (0.48 to 1.07)	NR	NR	NR

Abbreviations: AI, aromatase inhibitor; DFS, disease-free survival; HR, hazard ratio; NR, not reported; OFS, ovarian function suppression; Tam, tamoxifen.

*Analyzed for efficacy.

†Only the comparison between anastrozole and tamoxifen is presented (efficacy analysis for zoledronic acid *v* no adjuvant bisphosphonates is not reported).

‡Only the comparison of OFS + exemestane *v* OFS + Tam is presented (the Tam-alone arm of SOFT is not reported).

§Only the comparison of OFS + letrozole *v* OFS + Tam is presented (the OFS + letrozole + zoledronic acid arm is not reported).

of the study population), OFS had to be started concomitantly with cytotoxic therapy. Patients not receiving chemotherapy started oral endocrine therapy 6-8 weeks after GnRHa initiation. In the joint analysis of TEXT and SOFT, OFS plus exemestane was superior in terms of DFS to OFS plus tamoxifen without difference in OS.[30] The HOBOE trial was a three-arm study that randomly allocated premenopausal patients with hormone receptor–positive tumors to 5 years of OFS plus tamoxifen or letrozole or letrozole plus zoledronic acid.[37] The majority of patients (63%) received prior chemotherapy. The DFS benefit observed with OFS plus letrozole over tamoxifen was clinically meaningful but reached statistical significance only when combined with adjuvant bisphosphonates. No difference in OS was observed.[37]

On the basis of these data, current guidelines recommend the use of tamoxifen alone for women with low-risk of disease recurrence. For all other patients, particularly those deemed at sufficient risk to justify chemotherapy use, OFS should be considered but without clear preference and guidance on when to combine it with tamoxifen or an AI.[4,13,40-42]

Considering the impact of the toxicity profiles of the different treatments on the patients' quality of life, the available options should be clearly discussed with all women and may influence the final choice (Table 3).[29,43,44] Notably, up to 20%-25% of patients in the different trials opted for early cessation of endocrine treatment, with higher risk of nonadherence noted in women younger than age 35 years.[45] Hence, continuous monitoring of adverse events and compliance is crucial; switching to a different option when the ongoing therapy is not tolerated should be preferred over treatment cessation.

When counseling patients on the risk/benefit ratio of the proposed adjuvant treatments, together with the toxicity profile, it is crucial to provide precise information of individual prognosis and expected benefit of the proposed therapies. For premenopausal women with hormone receptor–positive/HER2-negative tumors, refining these estimations would be crucial not only to decide about chemotherapy use but also to distinguish between the different available adjuvant endocrine treatment options.

Refining Prognostication of Patients With Hormone Receptor–Positive/HER2-Negative Breast Cancer

Indication for adjuvant chemotherapy before endocrine treatment in patients with hormone receptor–positive/HER2-negative tumors represents one of the most challenging decisions in the breast cancer field. This is even more complex in premenopausal women because of the additional potential age-related negative consequences of chemotherapy.

In premenopausal patients with hormone receptor–positive/HER2-negative breast cancer without nodal involvement, a secondary analysis of TAILORx has recently provided important guidance on estimating chemotherapy benefit using the 21-gene assay.[22] Although no chemotherapy benefit is expected with an RS of 0-15, some benefit was observed in women age 50 years or younger with an RS of 16-25.[46] This benefit was mostly evident in premenopausal women older than age 45 years, suggesting a potential endocrine effect of chemotherapy mediated by the development of premature ovarian insufficiency, an adverse effect happening more frequently among older premenopausal women.[22] Additional dissection of the TAILORx cohort of women age 50 years and younger with an RS of 16 to 25 according to their clinical risk (defined by tumor size and histologic grade) showed a significant chemotherapy benefit in patients with an RS of 21-25 irrespective of their clinical risk (estimated absolute gain in distant recurrence at 9 years between 6.4% and 8.7%) as well as in those with an RS of 16-20 and high clinical risk (estimated absolute gain in distant recurrence at 9 years of 6.5%). Importantly, most of premenopausal patients received tamoxifen alone as adjuvant endocrine treatment; the absolute benefit observed with chemotherapy in TAILORx appears comparable to the one expected with OFS plus AI compared with tamoxifen alone in TEXT and SOFT. In patients with an RS of 16-20 and low clinical risk, no chemotherapy benefit was observed (estimated absolute gain in distant recurrence at 9 years of −0.2%).[22]

Despite providing robust prognostic information and prediction of chemotherapy benefit in patients with node-negative

TABLE 3. Main Results of the Patient-Reported Outcomes With the Different Available Adjuvant Endocrine Treatment Options for Premenopausal Patients

OFS + Tam (*v* Tam alone)	OFS + AI (*v* OFS + Tam)
↓ health-related QoL	≈ health-related QoL
↑ endocrine symptoms (hot flushes, sweats, sleep disturbance)	↓ hot flushes and sweats
↓ sexual functioning (vaginal dryness, difficulties in becoming aroused, decline in sexual interest)	↓ sexual functioning (vaginal dryness, difficulties in becoming aroused, decline in sexual interest)
↓ bone and joint pain	↑ bone and joint pain
↓ coping effort	
↑ treatment burden	

Abbreviations: AI, aromatase inhibitor; OFS, ovarian function suppression; QoL, quality of life; Tam, tamoxifen.

hormone receptor–positive/HER2-negative breast cancer, genomic tests have not been developed to select the most appropriate adjuvant endocrine treatment. The study by Pagani et al,[47] which accompanies this article, provides important data to guide and improve adjuvant endocrine treatment tailoring in premenopausal women with hormone receptor–positive/HER2-negative tumors. A secondary analysis of SOFT and TEXT was conducted to refine the estimates of the absolute magnitude of endocrine treatment effects in preventing distant recurrences according to patient prognosis. Classic clinicopathologic features (ie, age, tumor size, nodal status, grade, estrogen receptor level, progesterone receptor level, and Ki-67 expression level) were combined into a single continuous value named composite risk (ie, Regan risk score). Using the STEPP methodology, absolute treatment effects were investigated across the continuum of composite risk for 4,891 premenopausal women with hormone receptor–positive/HER2-negative breast cancer. The median follow-up was 9 years in TEXT and was 8 years in SOFT. The main messages from this analysis are the following: (1) in high-risk patients after chemotherapy, the higher the risk of recurrence, the larger the benefit expected with OFS plus exemestane compared with OFS plus tamoxifen or tamoxifen alone (estimated absolute gain in distant recurrence at 8 years up to 15%); (2) in low-risk patients without prior chemotherapy (overall 8-year freedom from distant recurrence ranging between 97% and 99%), there were no clinically relevant differences between the three endocrine treatment options (estimated absolute gain in distant recurrence at 8 years with OFS of approximately 1%); (3) in intermediate-risk patients, the benefit of OFS plus exemestane compared with OFS plus tamoxifen was more evident in the cohort of patients who did not receive chemotherapy (estimated absolute gain in distant recurrence at 8 years of up to 4%). Notably, selection of adjuvant chemotherapy in SOFT and TEXT was based on the same classic clinicopathologic features included in the Regan risk score (at that time, genomic tests were not widely available). On the basis of these data, together with the recent secondary analysis of TAILORx, clinicians now have valid tools to individualize and tailor the counseling of premenopausal women with hormone receptor–positive/HER2-negative breast cancer on the risk/benefit ratio of the proposed adjuvant treatments (Fig 1). Results of the RxPONDER trial (ClinicalTrials.gov identifier: NCT01272037) investigating the benefit of adding chemotherapy to different endocrine treatments in patients with one to three positive nodes and an RS of 25 or lower are awaited to further refine the counseling of the intermediate-risk population.

Practical Issues and Unanswered Questions

When the recent evidence on adjuvant endocrine treatment in premenopausal women is translated into clinical care, some practical issues and unanswered questions arise.

In premenopausal women receiving an AI as oral endocrine therapy, complete OFS must be obtained (although this is not required for tamoxifen). Combining a GnRHa with an AI is associated with more profound OFS than a GnRHa plus tamoxifen.[34,35] However, incomplete OFS is expected in approximately 20% of the patients receiving a GnRHa plus AI.[35] No prior exposure to chemotherapy, very young age, and high body mass index are potential risk factors for incomplete OFS to be considered during treatment decision making.[35,48] For the same reason, a GnRHa plus an AI is not the preferred choice for patients with compliance issues at risk for nonadherence to monthly injections. Importantly, when a GnRHa plus an AI is chosen, a continuous monitoring of treatment adherence and the possible occurrence of physiologic changes that suggest potential recovery of ovarian function (eg, cyclical fluctuation of climacteric symptoms and menstrual resumption) are crucial. Estradiol and FSH monitoring during treatment can be considered.[40,42,49] In the case of incomplete OFS during treatment with a GnRHa plus an AI, switching to tamoxifen (or bilateral oophorectomy) should be considered. The use of GnRH antagonists may partly overcome concerns about inadequate OFS[50]; future studies are awaited to define the role of GnRH antagonists in the adjuvant endocrine treatment of premenopausal patients.

The need to obtain complete OFS in patients receiving a GnRHa plus an AI may also impact the timing to start pharmacologic OFS and oral endocrine therapy. When chemotherapy is administered, concurrent administration of a GnRHa is safe[51,52] and is an effective strategy to reduce the risk of premature ovarian insufficiency.[52,53] This approach is endorsed by current guidelines.[4,40,42,54,55] Starting OFS before chemotherapy and continuing the treatment up to 5 years would also facilitate the choice of the oral endocrine therapy partner. If OFS is not given concurrently and chemotherapy-induced amenorrhea occurs, ovarian function should be constantly monitored, because it can resume even beyond 2 years after chemotherapy completion[56,57]; an AI alone in this setting should be avoided because of the significant risk of ovarian function recovery.[58]

Among the potential long-term negative consequences of OFS, especially when given concomitantly with an AI, particular attention should be given to bone loss. By reducing risk of skeletal complications and potentially improving survival outcomes,[36-38,59] prophylactic use of bisphosphonates can be considered in patients with treatment-related bone loss.[42,60,61]

Because of the significant risk of recurrence beyond 5 years after diagnosis,[62] extended adjuvant endocrine treatment is the standard of care for many patients with hormone receptor–positive breast cancer.[63] Premenopausal women have a higher risk of developing late recurrences[62] and appear to derive the greater benefit from extended adjuvant endocrine treatment.[64] Tamoxifen alone may be considered in women who remain premenopausal after the first 5 years of therapy, and an AI alone may be considered in those who become postmenopausal.[63] However, no

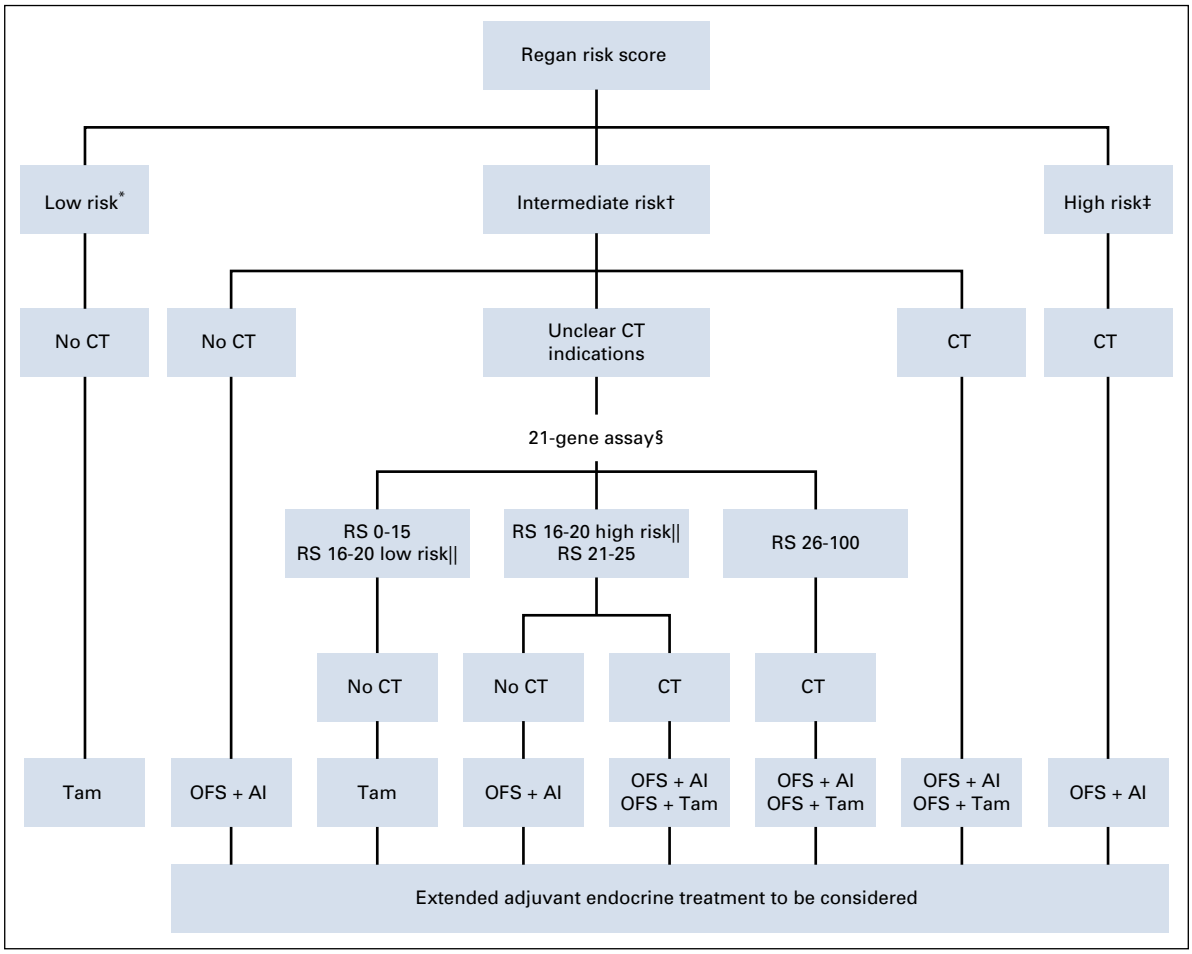

FIG 1. Proposed algorithm for the adjuvant treatment of premenopausal women with hormone receptor–positive/HER2-negative breast cancer, integrating the results obtained with the Regan risk score and the 21-gene assay for the intermediate-risk group. (*) Example of clinical case 1 (age 41 years; grade 1; pT1c pN0; estrogen receptor [ER] ≥ 50%; progesterone receptor [PR] ≥ 50%; Ki-67, 11%). (†) Examples of clinical case 2 (age 39 years; grade 2; pT1c pN0; ER approximately 50%; PR approximately 50%; RS of 21) and clinical case 3 (age 40 years; grade 2; pT1c pN1a; ER approximately 50%; PR approximately 50%). (‡) Example of clinical case 4 (age 39 years; grade 3; pT2 pN1a; ER, 95%; PR, 40%). (§) TAILORx provided data for patients with node-negative disease only; results of RxPONDER in patients with one to three positive nodes are awaited. (||) Low-risk was defined as tumor ≤ 3 cm and grade 1 or tumor ≤ 2 cm and grade 2 or tumor ≤ 1 cm and grade 3 (and when the low-risk criteria were not met, the clinical risk was defined as high). AI, aromatase inhibitor; CT, chemotherapy; OFS, ovarian function suppression; RS, recurrence score; Tam, tamoxifen.

evidence exists to decide the optimal approach for extending treatment in patients receiving OFS in the first 5 years.[65]

More evidence is needed to define the optimal adjuvant endocrine treatment of premenopausal (and postmenopausal) patients with hormone receptor–positive/HER2-positive breast cancer.[66-68] Subgroup analysis of the SOFT, TEXT, and HOBOE trials showed heterogeneity of treatment effect according to HER2 status and noted an apparent greater benefit from the addition of OFS and a lesser efficacy of AIs in patients with HER2-positive disease.[30,37] However, no strong conclusions can be derived because of the limited number of patients included who had HER2-positive disease and the lack of trastuzumab use for many of them. The Regan risk score did not include patients with HER2-positive disease.[47]

SUGGESTED APPROACHES TO MANAGEMENT

Several risk prediction models based on traditional clinicopathologic features have been developed to refine disease prognostication for patients and aid in treatment decision making.[69] However, the performance of these models in some patient subgroups, including premenopausal women, has been shown to be suboptimal.[69,70] In addition, the adjuvant endocrine treatment landscape for premenopausal women has been revolutionized so that reliable predictions about the expected benefit from adjuvant therapies in these patients have become difficult. By improving the stratification of patients' prognosis and the

quantification of treatment benefit, the Regan risk score (for which a Web application will be available online soon) has a major impact on clinical practice by allowing clearer counseling of the pros and cons of the proposed options; thus, the Regan risk score may be a valid tool to increase women's motivation to follow the prescribed treatment.[47] Recent data from TAILORx also suggest the possibility to better optimize chemotherapy indications for the cohort of patients with node-negative disease within the gray zone of the intermediate-risk category by the Regan risk score.[22] Taken together, these data have allowed another step toward improving adjuvant endocrine treatment tailoring for premenopausal patients (Fig 1).

Clinical case 1 reports about a patient who, after breast-conserving surgery, was diagnosed with a disease that can be defined as low risk (stage I, lymph node negative, grade 1, estrogen receptor/progesterone receptor strongly positive, Ki67 low) according to the Regan risk score without the need for genomic tests to make adjuvant treatment decisions. After multidisciplinary discussion, adjuvant radiotherapy and endocrine therapy with tamoxifen alone for 5 years was recommended.

Clinical case 2 is in the gray zone of the intermediate-risk category (stage I, lymph node negative, grade 2, estrogen receptor/progesterone receptor intermediate expression) by the Regan risk score, for which the 21-gene assay results is of added value to optimize disease management; with a RS of 21, we opted for anthracycline-free chemotherapy followed by OFS plus tamoxifen after discussion of the different toxicity profile of the two oral endocrine agents. However, during patient counseling, the potential overtreatment with chemotherapy administration and the possibility that the same benefit expected with adjuvant treatments could have been obtained by OFS plus an AI without prior chemotherapy was discussed.

Clinical case 3 falls also within the intermediate-risk category by the Regan risk score (stage II, one of three sentinel lymph nodes positive, grade 2, and estrogen receptor/progesterone receptor intermediate expression); the patient came to our center after receiving anthracycline-free chemotherapy. She resumed ovarian function after chemotherapy. We suggested the use of OFS with tamoxifen or an AI; after discussing the different toxicity profile of the two oral endocrine agents, the AI was preferred and started after the second administration of a GnRHa with estradiol and FSH monitoring every 3-6 months at least during the first year of treatment.

Clinical case 4 describes a high-risk patient according to the Regan risk score (stage II, three positive lymph nodes, grade 3, estrogen receptor strongly positive, progesterone receptor intermediate expression); without the need for genomic tests to make adjuvant treatment decisions, anthracycline- and taxane-based chemotherapy was recommended. The patient has three children but was concerned about risk of chemotherapy-induced premature ovarian insufficiency. A GnRHa was started 1 week before chemotherapy; an AI was added after the end of cytotoxic therapy with estradiol and FSH monitoring.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.02242.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Data analysis and interpretation: All authors
Collection and assembly of data: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Improving Adjuvant Endocrine Treatment Tailoring in Premenopausal Women With Hormone Receptor–Positive Breast Cancer

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No other potential conflicts of interest were reported.