Antihormones in Prevention and Treatment of Breast Cancer

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ABSTRACT: Breast cancer has the highest incidence of all types of cancer in women. Age and family history are the strongest risk factors, but sex hormones also play an important role, as demonstrated by epidemiological studies reporting a consistent association by reproductive personal history and breast cancer risk. The acceptability of preventive strategies by healthy women is closely related to their lifetime risk of developing breast cancer. Although surgical prevention may be considered in carriers of BRCA1/2 mutation, this option cannot be advocated for the majority of women whose risk is only moderately increased. In these women, chemoprevention with tamoxifen may reduce the incidence of estrogen receptor (ER)-positive breast carcinoma by 30–50%. Other drugs such as raloxifen and aromatase inhibitors (AIs) are currently being tested in this setting. Tamoxifen has been the most successful hormonal treatment over the last 30 years and, until recently, the most active drug in endocrine-sensitive breast cancer. In premenopausal breast cancer, tamoxifen still represents the therapy of choice, alone or in association with ovarian suppression. Conversely, in postmenopausal women it has been overtaken by third-generation AIs as first-choice drugs both in the adjuvant and metastatic settings. Many other issues, such as the optimal sequence between tamoxifen and AIs, the duration of AIs treatment, and the association of ovarian suppression and AIs in premenopausal patients still await the completion of randomized clinical trials. Furthermore, it is likely that treatment tailoring will be increased by the definition of patient subgroups that could derive larger benefits from AIs (progesterone receptor–negative, HER-2-overexpressing) or other new drugs.

KEYWORDS: breast; cancer; endocrine; treatment; prevention

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INTRODUCTION: RISK ASSESSMENT

Breast cancer has the highest incidence of all types of cancer in women and it is the second largest cause of cancer death in women.\(^1\) Therefore, all women can be considered at risk for breast cancer. Furthermore, only 20% of cases of breast cancer diagnosed in the age group of 30–50 years and one-third of those in women older than 50 years of age develop in women with one or more risk factor(s).

On the other hand, both age and family history are strong risk factors and may certainly help in selecting those women most likely to develop breast cancer. Many other risk factors confer a lower increase of the risk and are mainly related to women’s reproductive personal history such as age at menarche, menopause, and first pregnancy, breast feeding, and use of exogenous sex hormones.

The risk of developing breast cancer is perceived quite differently depending on whether it is presented in relative or absolute terms.\(^2\) As an example, a 40% increase in the risk of developing breast cancer associated with two daily alcoholic drinks sounds frightening, yet in absolute terms this translates to only one additional case of breast cancer occurring among about 1,500 women.\(^3\) Accordingly, the impressive 1 in 8 cumulative lifetime breast cancer risk of U.S. women only pertains to those who reach 75–80 years of age and escape other major causes of death (especially cardiovascular disease).

To overcome these problems, mathematical tools have been developed to project breast cancer risk over a definite period of time (usually 10 years). They take into account age, family history, reproductive factors and previous breast diseases,\(^4\) have been extensively validated, and may assist physicians and patients in decision-making on preventive or screening strategies.

Conversely, such models are not applicable to families with an unusual concentration of breast and ovarian cancer cases, in which the presence of a hereditary component, typically the mutation of the BRCA1/2 genes, can be suspected. Specific tools have been developed to assess the likelihood of detecting germ-line mutations (BRCA Pro, Cyrillic, etc) and to select the individuals at risk who are candidates for genetic testing.\(^5\)

It is increasingly clear that the genetic hereditability of breast cancer cannot be entirely ascribed to the mutation of single tumor-suppressor genes with high penetrance such as BRCA1/2, p53, or PTEN. Instead, many other genes with lower penetrance are likely implicated in determining the overall breast cancer risk, which could also be modified by reproductive or environmental factors. The most promising approach to assess this “background” genetic risk is represented by the simultaneous analysis of thousands of genes, with the definition of molecular signatures associated with different cancer risks (genomics, transcriptomics, proteomics).
PREVENTION

Lifestyle and/or environmental factors play an important role in influencing breast cancer risk. Their importance is suggested by the impressive difference in the incidence rates of populations living in undeveloped versus developed areas of the world, combined with the fact that the migration of individuals from low-risk populations to industrialized countries is associated with an increase of breast cancer risk in the next generation.

Many factors, such as physical exercise, low-fat diet, and reduction of alcohol use as well as early and/or multiple pregnancies, prolonged breast feeding, and avoidance of exogenous estrogens may account for at least part of these differences, while it is not clear whether environmental factors, apart from ionizing radiation, significantly increase the risk of the general population.

From the perspective of breast cancer prevention, it is likely that the adherence to strict dietary and reproductive habits to avoid these modifiable risk factors may actually reduce breast cancer incidence. Although the magnitude of the relative risk reduction is not expected to be great, if applied to the general population, this policy may well result in a significant number of cancers prevented. Nevertheless, this option may not be appealing to women who face an exceptionally increased breast cancer risk or who have already reached an age when the modification of such risk factors is no more possible or effective.6

For example, even accepting that appropriate lifestyle and reproductive choices may produce a 30% risk reduction, women with a BRCA1/2 mutation would still face a greater than 50% breast cancer lifetime risk. Therefore, prophylactic surgery (prophylactic mastectomy and/or oophorectomy) has been advocated in women at genetic risk and is currently pursued by an increasing percentage of healthy carriers.7

On the other hand, for most of the women generically defined “at risk” because they have one or two relatives with postmenopausal breast cancer or because of a previous biopsy for a proliferative benign breast disease, the lifetime risk of developing breast cancer is below 20%. For these large group of women, chemoprevention with “antihormones” is a feasible and attractive option.8

Tamoxifen

The selective estrogen receptor modulator (SERM) tamoxifen has been the most successful hormonal treatment and, until recently, the most active drug in estrogen receptor (ER)- and/or progesterone receptor (PR)-positive breast cancer.9 Since the publication of the ATAC trial with anastrozole,10 third-generation aromatase inhibitors (AIs) have overtaken tamoxifen as first-choice drug, both in the adjuvant and metastatic settings. Nevertheless, in the
preventive setting tamoxifen is the only approved drug and the only one for which large and long-term data are available.

The observed 53% decrease of contralateral disease in the early trials of adjuvant therapy included in the overview of the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) suggested the potential use of tamoxifen for breast cancer prevention.10 This finding prompted the launch of prospective randomized trials that specifically tested tamoxifen for breast cancer chemoprevention in healthy women.11–14

Although the small Royal Marsden11 and Italian trials 12 did not show a significant reduction of breast cancer incidence, both the large NSABP-P113 and IBIS-I14 trials clearly showed that tamoxifen may indeed prevent breast cancer. A summary of all trials showed a 34% reduction of overall breast cancer incidence (invasive and noninvasive, ER-positive and -negative, pre- and postmenopausal) (TABLE 1).

As expected, no protection was conferred against ER-negative tumors (hazard ratio [HR] 1.22, 95% confidence interval [CI] 0.89–1.67; \( P = 0.21 \)), while ER-positive cancers were decreased by 48% (95% CI 36–58; \( P < 0.0001 \)). Conversely, age did not affect the degree of breast cancer reduction (HR 0.66; 95% CI 0.52–0.85 for age <50 years vs. HR 0.63; 95% CI 0.51–0.77 for age ≥50 years; \( P = 0.96 \)). Tamoxifen increased both endometrial cancer (HR 2.4; 95% CI 1.5–4.0; \( P = .0005 \)) and venous thromboembolic events (HR 1.9; 95% CI 1.4–2.6; \( P < 0.0001 \)) with similar relative risks, but higher absolute risks among older women. Finally, no effect was observed in non-breast cancer mortality.15

The lower protection reported in the European IBIS-1 trial as compared to the American NSABP-P1 trial accounts for the fact that in Europe tamoxifen is not yet recommended as a preventive agent, except in women at very high breast cancer risk without significant comorbidities, while in the United States this indication has received the Food and Drug Administration’s (FDA) approval.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>No. Randomized</th>
<th>No. of Breast Cancers</th>
<th>Hazard Ratio</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal Marsden (11)</td>
<td>High-risk, family history</td>
<td>2471</td>
<td>62 vs. 75</td>
<td>0.83</td>
<td>ns</td>
</tr>
<tr>
<td>Italian (12)</td>
<td>Normal-risk, hysterectomy</td>
<td>5408</td>
<td>34 vs. 45</td>
<td>0.76</td>
<td>ns</td>
</tr>
<tr>
<td>NSABP-P1 (13)</td>
<td>&gt;1.6% 5-year risk</td>
<td>13 388</td>
<td>124 vs. 244</td>
<td>0.51</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td>IBIS-I (14)</td>
<td>&gt;2-fold relative risk</td>
<td>7139</td>
<td>69 vs. 101</td>
<td>0.68</td>
<td>.013</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>28 356</td>
<td>289 vs. 465</td>
<td>0.66</td>
<td>.0007</td>
</tr>
</tbody>
</table>

ns = not significant.
Raloxifene

Several clinical trials have demonstrated that raloxifene, a second-generation SERM, is effective in the prevention and treatment of osteoporosis. Furthermore, these trials, as well as preclinical models, suggested that raloxifene may also reduce breast cancer risk in postmenopausal women.

The Multiple Outcomes Raloxifene Evaluation (MORE) study is a multicenter, randomized, placebo-controlled, double-blind clinical trial that was designed to test whether 60–120 mg/day of raloxifene for 4 years could reduce the risk of fracture in 7,705 postmenopausal women with osteoporosis. At 36 months of follow-up, the risk of vertebral fractures was reduced by 30%; among the secondary endpoints, the study showed an impressive 72% reduction in the risk of ER-positive invasive breast cancer, with no apparent decrease in the incidence of ER-negative tumors. Like tamoxifen, raloxifene increased the risk of pulmonary embolism (RR, 3.0; 95% CI, 1.2–9.3) and deep venous thrombosis (RR, 1.6; 95% CI, 0.91–2.86) as compared to placebo. Conversely, the risk of endometrial cancer was not affected by raloxifene use.

Participants in the MORE trial who agreed to continue therapy were entered in the Continuing Outcomes Relevant to Evista (CORE) trial; the primary endpoint of this study was to assess the incidence of invasive breast cancer after 4 additional years of raloxifene. The risk of invasive breast cancer among the 5,213 participants in the CORE trial was reduced by 69% (HR 0.31; 95% CI, 0.24–0.71), while the study confirmed the increase of thromboembolic events (HR 2.17; 95% CI, 0.83–5.70) and the null effect on endometrial risk associated with raloxifene use.

The results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) Study of Tamoxifen and Raloxifene (STAR) trial were published early this year. This was a prospective, double-blind, randomized clinical trial of 5 years of tamoxifen versus 5 years of raloxifene in 19,747 postmenopausal women of a mean age of 58.5 years, with increased 5-year breast cancer risk. No differences were observed between the tamoxifen and raloxifene arms in the number of invasive breast cancers (163 vs. 168, risk ratio [RR], 1.02; 95% CI 0.82–1.28), but tamoxifen was associated with a lower incidence of noninvasive breast cancer (57 vs. 80; RR, 1.40; 95% CI, 0.98–2.00). In the raloxifene arm there were fewer endometrial cancers (36 vs. 23 cases; RR, 0.62; 95% CI, 0.35–1.08) and thromboembolic events (RR, 0.70; 95% CI, 0.54–0.91) and similar osteoporotic fractures. Finally, no difference was reported in the total number of deaths (101 vs. 96 for tamoxifen vs. raloxifene).

In the Raloxifene Use for The Heart (RUTH) Trial, 10,101 postmenopausal women with coronary heart disease (CHD) or multiple risk factors for CHD were randomized to 60 mg of raloxifene daily or placebo and followed for a median of 5.6 years. The two primary outcomes were coronary events and invasive breast cancer. Raloxifene reduced the risk of invasive breast cancer (HR 0.56; 95% CI, 0.38–0.83), but not the risk of primary coronary events.
(HR 0.95; 95% CI, 0.84–1.07). Deaths from any cause or total stroke did not vary according to group assignment, but raloxifene was associated with an increased risk of fatal stroke (HR 1.49; 95% CI 1.00–2.24) and venous thromboembolism (HR 1.44; 95% CI 1.06–1.95).²⁰

If raloxifene obtains FDA approval for chemoprevention after the publication of these studies, it is likely that many women will be willing to take it in the light of its perceived more favorable risk/benefit profile as compared to tamoxifen.

**Aromatase Inhibitors**

All three major trials comparing various AIs with tamoxifen as adjuvant treatment for invasive breast cancer have reported significant reductions in the risk of contralateral cancer favoring AIs¹⁰,²¹,²² (Table 2) and similar results were reported by two other trials also.²³,²⁴

Furthermore, AIs were associated with fewer thromboembolic events and cases of endometrial cancer, whereas, as expected, musculoskeletal disorders and fractures occurred at a significantly higher rate with AI. Lower contralateral breast cancer rates (14 vs. 26, *P*-value not reported) were also found in the MA.¹⁷ adjuvant trial of extended endocrine therapy with 5 years of letrozole after 5 years of tamoxifen versus 5 years of tamoxifen in ER+ breast cancer.²⁵

No clinical controlled trials have been yet published with AIs in a preventive setting. The IBIS-II trial is an ongoing large international randomized trial consisting of two substudies designed around different high-risk populations. One of them (treatment) will compare anastrozole versus tamoxifen for 5 years in 4,000 women who undergo breast-conserving surgery for ductal carcinoma *in situ* (DCIS), whereas the other (prevention) will compare anastrozole versus placebo for 5 years in 6,000 women classified at “high-risk” according to several risk factors, including a previous DCIS treated with mastectomy.²⁶

**Aromatase Inhibitors plus Other Drugs**

The steroidal third-generation AI exemestane is currently being tested by the National Cancer Institute of Canada in the Mammary Prevention 3 trial, which will randomly assign 5,100 high-risk postmenopausal women to placebo versus exemestane versus exemestane plus celecoxib. Celecoxib is a COX-2 inhibitor that belongs to the family of nonsteroidal anti-inflammatory drugs (NSAIDs). Actually, aspirin and NSAIDs indirectly inhibit estrogen biosynthesis by reducing the synthesis of prostaglandins, which in turn stimulate aromatase gene expression.²⁷ Although prospective controlled trials are still lacking, both epidemiological and biological studies support the potential activity of this class
of drugs for the prevention of ER+ breast tumors.\textsuperscript{28,29} Conversely, clinical trials are under way for ER– tumors to test drugs whose mechanism of action is not directed to interfere with the estrogenic pathways, such as ornithine decarboxylase inhibitors, retinoids, and statins.\textsuperscript{30}

**TREATMENT**

Estrogenic deprivation is a key element of breast cancer treatment. Clinical evidence on the role of estrogens in breast cancer progression was provided as early as in 1886 by Sir George Beatson, who demonstrated that surgical oophorectomy was able to provide tumor regression in patients with locally advanced breast cancer.\textsuperscript{31} This pivotal observation and the discovery of estrogen receptors\textsuperscript{32} were instrumental in the development of many endocrine treatments over the last 50 years, among which tamoxifen has been the most successful.\textsuperscript{33}

**Tamoxifen**

Tamoxifen is a SERM approved by the FDA in 1977 for the treatment of women with advanced breast cancer. Although many of its properties are still not fully elucidated, tamoxifen binds the nuclear ER and exerts estrogen-antagonist activity in breast tissue thus inhibiting tumor growth. On the other hand, tamoxifen has an estrogen-agonistic effect on bone and serum lipid concentrations, which accounts for its protective effect against osteoporosis in postmenopausal women and, possibly, against cardiovascular diseases, whereas its ability to stimulate the endometrium is associated with an increase of endometrial cancer risk.

According to the latest overview of the EBCTCG,\textsuperscript{34} about 5 years of adjuvant tamoxifen reduce the annual relapse and death rates in ER+ tumors by 40% and 31%, respectively. This effect is largely irrespective of the use of chemotherapy, age, progesterone receptor status, or other tumor characteristics and persists after discontinuation of therapy (“carry-over effect”), so that the cumulative reduction in mortality is more than twice as large at 15 years as at 5 years after diagnosis. The most serious side effects of tamoxifen are the increase of thromboembolic events (about two times) and endometrial cancer (almost three times), although mortality due to these events or any other non-breast cancer-related event is not significantly different among tamoxifen and non-tamoxifen users.

As far as the issue of duration is concerned, the results of the NSABP B-14 trial\textsuperscript{35} suggest that there is no benefit in continuing tamoxifen beyond 5 years of therapy, although only the completion of the large ATLAS (Adjuvant Tamoxifen—Longer against Shorter) and aTTom (Adjuvant Tamoxifen Treatment Offer More?) trials will allow definite conclusions to be drawn.
<table>
<thead>
<tr>
<th>Study</th>
<th>ATAC\textsuperscript{10}</th>
<th>IES\textsuperscript{21}</th>
<th>BIG 1 –98\textsuperscript{22}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>9,366 postmenopausal women with HR + or HR</td>
<td>4,742 postmenopausal women with HR + or HR</td>
<td>8,010 postmenopausal women with HR+ breast cancer following primary surgery and chemotherapy</td>
</tr>
<tr>
<td></td>
<td>unknown breast cancer following primary surgery and chemotherapy</td>
<td>unknown breast cancer following completion of 2–3 years of tamoxifen</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>A vs. T for 5 years</td>
<td>T for 2–3 years followed by E vs. T continued for 5 years</td>
<td>L vs. T for 5 years</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>68 months</td>
<td>30.6 months</td>
<td>25.8 months</td>
</tr>
<tr>
<td>Contralateral breast cancer</td>
<td>35 vs. 59, 42% reduction; ( P = 0.01 )</td>
<td>9 vs. 20, 56% reduction</td>
<td>16 vs. 27, 41% reduction</td>
</tr>
<tr>
<td></td>
<td>(only HR+ patients: 53% reduction; ( P = 0.001 ))</td>
<td>( P = 0.00005 )</td>
<td>( P = \text{not reported} )</td>
</tr>
</tbody>
</table>

A = anastrozole; T = tamoxifen; L = letrozole; E = exemestane; HR = hormone receptors.
Ovarian Ablation/Suppression

As already recalled, ovarian ablation was the first systemic treatment for breast cancer to be introduced, and several randomized trials in the adjuvant setting have been conducted over the last 50 years. The EBCTCG meta-analysis of these trials clearly established that ovarian ablation/suppression among women less than 50 years of age at the time of treatment is associated with significant improvement in recurrence-free (17%; \( P = 0.00001 \)) and overall survival (13%; \( P = 0.004 \)) after 15 years of follow-up.\(^{34} \) No difference was reported whether ovarian ablation/suppression was induced by surgery or radiotherapy or achieved with luteinizing hormone- or gonadotropin hormone-releasing hormone (LHRH or GnRH) agonists.

Although these gains may appear relatively small in absolute terms (4.3% and 3.2% respectively), it must be emphasized that 63% of the participants were ER-untested, and thus at least some ER-negative patients were included in these trials. Furthermore, a considerable proportion of women also received chemotherapy, which is known to reduce the benefit of other ovarian treatments through its toxic effect on ovarian activity. For instance, in the absence of chemotherapy, ovarian ablation/suppression was associated with a 25.7% (\( P = 0.0005 \)) and 24.7% (\( P = 0.0006 \)) reduction in the odds of recurrence and death, respectively, whereas the corresponding figures were 10% (\( P > 0.1 \)) and 8% (\( P > 0.1 \)) in the presence of chemotherapy. Accordingly, the benefit of adding ovarian ablation after chemotherapy was lower in the older (40–49 years) as compared to the younger (<40 years) premenopausal patients (ratio 0.95 vs 0.86, respectively) since the former experience higher rates of permanent ovarian suppression as a consequence of cytotoxic treatments.

Several head-to-head comparisons between chemotherapy and ovarian ablation showed that goserelin for 2 years is equivalent\(^{36,37} \) or superior\(^{38} \) to cyclophosphamide, methotrexate, and fluorouracil (CMF) for six courses in ER-positive patients, but inferior for the ER-negative population.

Ovarian Ablation/Suppression plus Tamoxifen

In premenopausal women with ER-positive advanced breast cancer, a meta-analysis of four clinical trials showed that the combined treatment of LHRH agonist plus tamoxifen confers a significant benefit in survival (\( P = 0.02 \)), progression-free survival (\( P = 0.0003 \)), and overall response rate (\( P = 0.03 \)) over tamoxifen alone.\(^{39} \)

In the adjuvant setting, several studies reported similar\(^{40} \) or better\(^{41} \) outcome with LH-RH agonist plus tamoxifen as compared to CMF or anthracyclin-based combinations.\(^{42} \) According to the Intergroup Trial 0101, in premenopausal, node-positive, ER-positive patients who received six courses of CMF, the addition of LH-RH inhibition alone after chemotherapy confers no benefit, whereas the combination of LH-RH inhibition plus tamoxifen does.\(^{43} \) Conversely, in
the Zoladex in Premenopausal Patients (ZIPP) trial, the association of LH-RH inhibition and tamoxifen for 2 years was superior to tamoxifen alone for 2 years and no endocrine therapy.44

Taken together, these results suggest that ovarian inhibition in ER-positive breast cancer is at least as effective as chemotherapy. Furthermore, the contribution of ovarian inhibition is higher in the absence of previous chemotherapy or concomitant tamoxifen administration and also in the younger (\(< 40 \text{ years of age}\)) patients, irrespective of the combination with other adjuvant treatments.45

**Aromatase Inhibitors**

Several phase III studies demonstrated that third-generation AIs are superior to tamoxifen as first-line therapy for metastatic breast cancer in postmenopausal women, with longer time to progression (anastrozole),46 time to treatment failure (exemestane),47 and survival (letrozole).48

The success of these early trials led to the comparison of AI against tamoxifen in the adjuvant setting either as single agents or given in combination or sequentially after tamoxifen (TABLE 3). Results from the three following strategies have been already published: (a) “upfront,” comparing tamoxifen versus AIs as initial therapy for 5 years10,22; (b) “switch,” comparing tamoxifen for 5 years versus tamoxifen for 2–3 years followed by AIs for 2–3 years21,24; and (c) “extended adjuvant,” comparing tamoxifen for 5 years versus tamoxifen for 5 years followed by AIs for 5 years.25

With the notable exception of the combined therapy arm (anastrozole + tamoxifen) in the ATAC trial,10 AIs showed superiority against tamoxifen in all of these trials, irrespective of study design, nodal status, and previous chemotherapy, with longer disease-free survival (TABLE 3) and time to distant metastasis rates. Although several thousands of patients have been involved in these trials, none of them has yet reached a sufficient number of events to demonstrate a significant overall survival benefit over tamoxifen.

A survival advantage for AI is expected to show up with longer follow-up also in the light of their favorable safety profile (fewer venous thromboembolic and ischemic cerebrovascular complications and endometrial cancer risk). The only worrying side effect associated with AI use is represented by a 50% increase in bone fractures, especially when compared with the positive effect of tamoxifen on bone mineral density.50 More controversial is the potential detrimental effect of AI on serum lipids (especially hypercholesterolemia), which in turn could lead to an increase in deaths from cerebrovascular accident and cardiac incidents, as reported in the BIG 1-98 trial (7 vs. 1 and 13 vs. 6, respectively).49 Finally, another minor characteristic and yet unexplained side effect of AIs is represented by musculoskeletal symptoms, whereas gynecological symptoms (endometrial polyps, vaginal discharge, and bleeding) are significantly lower as compared to occurring those with tamoxifen in all trials.
### TABLE 3. Comparison of six adjuvant trials with aromatase inhibitors

<table>
<thead>
<tr>
<th>Design</th>
<th>ATAC&lt;sup&gt;9&lt;/sup&gt;</th>
<th>BIG 1-98&lt;sup&gt;22&lt;/sup&gt;</th>
<th>ARNO 95/ABCSG 8&lt;sup&gt;24&lt;/sup&gt;</th>
<th>ITA&lt;sup&gt;23&lt;/sup&gt;</th>
<th>IES&lt;sup&gt;21&lt;/sup&gt;</th>
<th>MA 17&lt;sup&gt;25&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A vs. T vs. AT × 5 yr, upfront</td>
<td>L vs. T × 5 yr, upfront</td>
<td>T→A vs. A, 5 yr, switch</td>
<td>T→A vs. A, 5 yr, switch</td>
<td>T→E vs T, 5 yr, switch</td>
<td>T × 5 years vs. T→L × 10 yr, extended</td>
</tr>
<tr>
<td>No. of patients</td>
<td>6,186</td>
<td>8,010</td>
<td>3,224</td>
<td>448</td>
<td>4,742</td>
<td>5,187</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>68</td>
<td>25.8</td>
<td>28</td>
<td>36</td>
<td>30.6</td>
<td>30</td>
</tr>
<tr>
<td>No. of events</td>
<td>1,226</td>
<td>647</td>
<td>177</td>
<td>45</td>
<td>449</td>
<td>247</td>
</tr>
<tr>
<td>Absolute benefit in DFS</td>
<td>3.7%</td>
<td>2.6%</td>
<td>3.1%</td>
<td>8.8%</td>
<td>4.7%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

DFS = disease-free survival; No. = number; yr = years; A = anastrozole; T = tamoxifen; L = letrozole; E = exemestane.
Many issues remain unresolved, such as the existence of a group of patients more likely to benefit from an upfront treatment with AIs. The latter hypothesis is supported by adjuvant and neoadjuvant studies, where the advantage of AIs over tamoxifen is particularly evident during the first 2–3 years of follow-up in PR-negative tumors\textsuperscript{51} or in the presence of oncogene HER-2 overexpression.\textsuperscript{52}

**CONCLUSION**

All variables that modify the exposure to endogenous or exogenous estrogens are known to influence a woman’s lifetime risk of developing breast cancer. Given the availability of effective drugs like LH-RH analogues, SERMs, and AIs to prevent ER-positive cancers, more accurate methods must be developed to predict which high-risk women are most likely to develop this type of tumor.

Endocrine sensitivity has a major role in determining the chance of cure of breast cancer: according to recent microarray data, this single parameter discriminates truly different breast tumors. As a consequence, although the prognostic value of ER/PR expression is only weak, its predictive value is very strong and accounts for the overall more favorable prognosis of endocrine-sensitive tumors.

In premenopausal patients with ER/PR-positive disease, the benefit of the combination of ovarian ablation and tamoxifen is comparable to that of chemotherapy, while data are accumulating on the efficacy of the association of ovarian ablation plus AIs. In perimenopausal women, the sequential therapy with tamoxifen for 2–3 years followed by AIs is probably the most reasonable option, whereas in truly postmenopausal women the upfront treatment with AI is supported by their superior activity and more favorable side-effect profile.

With the advent of new alternatives to tamoxifen, the issue of the optimal duration of endocrine treatment is being investigated in several clinical trials, but in high-risk patients who completed 5 years of tamoxifen, the addition of further 5 years of letrozole may already be considered as the standard of care. Moreover, bisphophonates are effective and safe drugs to counterbalance the loss of bone density and the consequent increase of osteoporotic fractures associated with AIs.

The future of breast cancer endocrine therapy, as well as that of many other oncological treatments, is directed to improve our way to “tailor” medical decisions by decrypting the specific “biological portrait” of each tumor. Toward this aim, it will be essential that the impressive improvements already achieved in the molecular characterization of the disease be backed by the development of new effective drugs.

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