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REVIEW ARTICLE

Aromatase inhibitors in premenopausal women with breast cancer: the state of the art and future prospects

M. Pistelli MD,* A. Della Mora MD,* Z. Ballatore MD,* and R. Berardi MD*

ABSTRACT

Approximately 11% of patients with breast cancer (BCa) are diagnosed before menopause, and because in most of those patients the tumour expresses a hormone receptor, treatment with endocrine interventions can be applied in any setting of disease (early or advanced). In the past, hormonal treatment consisted only of the estrogen receptor modulator tamoxifen, associated with luteinizing hormone–releasing hormone (LHRH); more recently, aromatase inhibitors (AIs) have come into widespread use. The AIs interfere with the last enzymatic step of estrogen synthesis in which androgens are converted into estrogens. Initially, the AIs were used alone in postmenopausal patients to prevent disease recurrence, but together with LHRH analogs, they can be used in premenopausal patients to produce better estrogen suppression than can be achieved with tamoxifen plus a LHRH analog. Using a systematic review of the scientific literature (prospective and retrospective studies), we set out to assess the efficacy of AIs compared with other endocrine therapy in various disease settings (neoadjuvant, adjuvant, metastatic).

Key Words Breast cancer, aromatase inhibitors, premenopausal women, tamoxifen, LHRH analog, letrozole, anastrozole, exemestane

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INTRODUCTION

Hormone receptor–positive (HR+) breast carcinoma represents the most frequent subtype of breast cancer (BCa) around the world and in all age groups[1]. It is estimated that, among women with BCa, 60%–75% have estrogen receptor (ER)–positive disease, and 65% of those women have tumours that also express the progesterone receptor (PgR)[2–5]. Approximately 11% of patients with BCa are diagnosed before the age of 45 years[6] (premenopausal), and most of those women have HR+ breast tumours: 51.4% in patients less than 35 years of age rising to 67.6% in patients 40–44 years of age[7–9]. Breast cancers that are ER- or PgR-positive (or both) benefit from endocrine interventions, which represent the mainstays of treatment for either early or advanced HR+ disease[10,11], making such treatments the most widely prescribed in this setting in the world[12].

The selective ER modulator tamoxifen has been in use for years, and its benefits as adjuvant therapy were shown in the first Early Breast Cancer Trialists' Collaborative Group meta-analysis and were confirmed in subsequent meta-analyses[13–15]. Compared with no endocrine therapy, tamoxifen was associated with a reduction in BCa recurrence of 39% (relative risk: 0.61; $p < 0.00001$) and in mortality of about one third (relative risk: 0.70; $p < 0.00001$) throughout the first 15 years[15]. Tamoxifen could also be a choice in premenopausal patients with metastatic BCa, for whom endocrine therapy should be preferred in HR+ disease, unless endocrine resistance or visceral crisis has developed. A meta-analysis showed significantly better outcomes for tamoxifen plus a LHRH analog than for tamoxifen alone[16].

A few years ago, third-generation aromatase inhibitors (AIs) were introduced as an alternative to tamoxifen or in sequence after tamoxifen, initially for postmenopausal patients[17]. Trials have directly compared tamoxifen with AIs up front, as sequential therapy (tamoxifen followed by an AI), and in extended AI use. In postmenopausal women, prevention of disease recurrence is better with AIs than with tamoxifen. The Early Breast Cancer Trialists' Collaborative Group conducted a meta-analysis of randomized trials of AIs compared with tamoxifen monotherapy that showed a significant reduction in recurrence, but not in BCa mortality with the AIs[18].

Correspondence to: Arianna Della Mora, Clinica di Oncologia Medica, Università Politecnica delle Marche, AO Ospedali Riuniti-Ancona, Via Conca n 71, Ancona 60126 Italy.
E-mail: arianna.dellamora@gmail.com **DOI:** https://doi.org/10.3747/co.25.3735

The AIs interfere with aromatization of the A-cycle of steroids, which leads to the conversion of androgens into estrogens[17,19]. Accordingly, AIs lower only extra-ovarian estrogen production. In premenopausal women, AIs reduce the feedback from extra-ovarian estrogens to the hypothalamus and pituitary gland. The subsequent gonadotropin secretion increases ovarian stimulation[20], which is why AIs must be combined with LHRH analogs to accomplish complete blockade of ovarian and peripheral estrogen synthesis, leading to a postmenopausal-like plasma estrogen concentration[20]. Thus, estrogen suppression in premenopausal patients with early BCa is more intense when the patient receives AIs plus gonadotropin (GN)–RH analog than when she receives tamoxifen plus GnRH[21].

Ovarian suppression can also be achieved by ovarian surgical ablation or irradiation; however, pharmacologic ovarian suppression (using monthly or 3-month intramuscular injections of LHRH analog) actually represents the cornerstone of a hormonal strategy because it is less invasive than the other options and has similar efficacy. Furthermore, because of young age and the aggressive pattern of BCa, many premenopausal patients undergo adjuvant chemotherapy before starting hormonal treatment; chemotherapy (especially regimens containing alkylating agents as cyclophosphamide) can be associated with an amenorrhea that is very difficult to distinguish from physiologic menopause. Moreover, it is possible, even if it is not a standard, to begin ovarian function suppression with a LHRH analog before starting chemotherapy to preserve gonadal function and fertility in very young BCa patients[22]; however, that approach can complicate evaluation of the patient's menopausal state. Thus, all current principal guidelines are consistent in recommending evaluation of menopausal status before chemotherapy starts, so that the best hormonal therapy can be chosen.

Experience in using AIs combined with ovarian function suppression in premenopausal women with advanced BCa is still limited.

We systematically reviewed the scientific literature for prospective and retrospective studies assessing the efficacy of AIs compared with other endocrine therapy in various disease settings (neoadjuvant, adjuvant, metastatic).

METHODS

Combinations of the key words "aromatase inhibitors," "premenopausal breast cancer," "early breast cancer," "advanced breast cancer," "letrozole," "anastrozole," "exemestane," and "LHRH analogue" were used to search the literature for prospective randomized clinical trials and retrospective studies examining AIs in premenopausal women with BCa in various settings. Major ongoing and unpublished clinical trials were identified by researching current trials at http://ClinicalTrials.gov. Tables I–III summarize the chosen trials.

RESULTS

AIs As Neoadjuvant Endocrine Therapy in Premenopausal BCa

Very little evidence has been generated about the role of AIs in the neoadjuvant setting in premenopausal women. This field of research is intriguing, considering that preoperative chemotherapy seems to be less effective in HR+ BCa[34,35]. Some authors began to think of endocrine therapy as an alternative approach, especially for BCa patients with inoperable disease and contraindications to chemotherapy.

Torrisi *et al.*[23] retrospectively studied the activity of letrozole plus a GnRH analog as neoadjuvant treatment in 32 premenopausal women with T2–4b BCa whose tumours showed expression of ER and PgR in more than 10% of cells. Endocrine therapy consisted of ovarian suppression using a GnRH analog. After obtaining a postmenopausal level of circulating estradiol, the AI letrozole was added for at least 3 months. Estradiol and gonadotrophin levels were checked monthly to verify ovarian suppression. Only 1 patient achieved a complete clinical response; 15 patients (47%) achieved clinical and imaging partial responses, for an overall response rate of 50%. At the time of surgery, all tumours were still ER-positive; downregulation of PgR was observed in 26 patients. Endocrine therapy also induced downregulation of proliferative activity: only 9 patients (28%) had a Ki-67 index exceeding 20% at surgery; 17 patients (53%) had shown high proliferative activity at their initial biopsy. After a median follow-up of 3 years, the overall disease-free survival (DFS) was 76% [83% in clinical responders, 70% in non-responders; 95% confidence interval (CI): 59% to 93%]. Those results are encouraging and certainly have to be confirmed by further data.

AIs As Adjuvant Endocrine Therapy in Premenopausal BCa

After AIs were demonstrated to be superior to tamoxifen in postmenopausal patients, some studies began to consider those agents in premenopausal patients to determine whether AIs combined with a LHRH analog could better reduce the risk of recurrence.

In 2009, Gnant *et al.*[24] compared tamoxifen plus a LHRH analog with AI plus a LHRH analog, both with or without zoledronic acid, as adjuvant treatment for HR+ BCa. The primary endpoint was DFS; recurrence-free survival and overall survival (OS) were secondary endpoints. The study enrolled 1083 patients (median age: 45 years); goserelin was given with tamoxifen or with anastrozole, both taken daily for 3 years. At the median follow-up of 47.8 months, no significant difference in DFS was observed between the tamoxifen and anastrozole groups (DFS rate: 92.8% vs. 92.0%; 95% CI: 0.78 to 1.53; $p = 0.59$). The lack of a significant difference persisted even at the final analysis, after a median of 94.4 months' follow-up[25]. No significant difference was observed between the hormonal therapies in term of recurrence-free survival and OS. Overall, the two groups did not significantly differ with respect to the serious adverse events evaluated (occurring in 10% or fewer of the women). Uterine polyps were the only events that occurred more frequently during treatment with tamoxifen (8.9% vs. 1.5%; $p < 0.001$)[24]. Arthralgia and bone pain occurred more frequently in women taking anastrozole.

More recently, results of the TEXT and SOFT trials have been published. The phase III TEXT trial compared exemestane plus ovarian suppression with tamoxifen plus ovarian suppression for 5 years in premenopausal women with HR+ early BCa. Ovarian suppression was achieved

TABLE I Study of aromatase inhibitors in the neoadjuvant setting

Reference	Setting	Pts (*n*)	Study design	Treatment arms	Primary endpoint	*p* Value
Torrisi *et al.,* 2007[23]	Locally advanced operable disease (primary therapy)	35	Prospective	Single-arm	Clinical response (50%)	—

Pts = patients.

TABLE II Studies of aromatase inhibitors (AIs) in the adjuvant setting

Reference	Setting	Pts (*n*)	Study design	Treatment arms	Primary endpoint	*p* Value
Gnant *et al.,* 2009[24], Gnant *et al.,* 2015[25]	Early	1803	Prospective	4 arms: No LH-RHa, tamoxifen LH-RHa, tamoxifen, and ZA LH-RHa, AI LH-RHa, AI, ZA	Disease-free survival	0.59 (comparing AI with tamoxifen) 0.01 (comparing ZA with no ZA)
Pagani *et al.,* 2014[26]	Early	4690	Prospective	Two arms: Ovarian suppression plus ... Exemestane or Tamoxifen	Disease-free survival: 91.1% Exemestane arm 89.7% Tamoxifen arm	<0.001

Pts = patients; LH-RHa = luteinizing hormone–releasing hormone analog; ZA = zoledronic acid.

TABLE III Studies of aromatase inhibitors in the advanced setting

Reference	Setting	Pts (*n*)	Study design	Treatment arms	Primary endpoint	*p* Value
Forward *et al.,* 2004[27]	Advanced	16	Prospective	Single-arm	Clinical benefit 75%	
Carlson *et al.,* 2010[28]	Advanced	35	Prospective	Single-arm	Objective response rate 37.5%	
Cheung *et al.,* 2010[29]	Advanced	36	Prospective	Single-arm	Clinical benefit 67%	
Park *et al.,* 2010[30]	Advanced	73	Prospective	Two arms: Premenopausal patients Postmenopausal patients	Response rate and clinical benefit	0.09 0.77
Yao *et al.,* 2011[31]	Advanced	52	Retrospective	Single-arm	Progression-free survival	
Liu *et al.,* 2013[32]	Advanced	35	Retrospective	Single-arm	Objective response rate and clinical benefit	
Nishimura *et al.,* 2013[33]	Advanced	37	Prospective	Single-arm	Response rate	0.006

Pts = patients.

using triptorelin (or bilateral oophorectomy or ovarian irradiation after at least 6 months of triptorelin). In the phase III SOFT trial, premenopausal women with early BCA were randomized to receive 5 years of adjuvant treatment with exemestane plus ovarian suppression, with tamoxifen plus ovarian suppression, or with tamoxifen alone; ovarian suppression was obtained using triptorelin, bilateral oophorectomy, or ovarian irradiation. The primary endpoint was DFS.

A joint analysis of TEXT and SOFT at the median follow-up of 68 months revealed a better 5-year DFS for patients who received exemestane plus ovarian suppression than for patients who received tamoxifen plus ovarian suppression (91.1% vs. 87.3%; hazard ratio: 0.72; 95% CI: 0.60 to 0.85; $p < 0.001$). The OS was not significantly different between the groups[26].

Patients treated with exemestane plus ovarian suppression more frequently experienced musculoskeletal symptoms and fractures as main adverse events because of a higher incidence of osteoporosis (T score less than –2.5: 13.2% vs. 6.4%). Thromboembolic accidents occurred at a higher incidence rate in patients who received tamoxifen plus ovarian suppression. Patients completed a quality-of-life questionnaire: compared with those receiving

exemestane plus ovarian suppression, those receiving tamoxifen plus ovarian suppression more frequently reported hot flushes and sweating, although those symptoms improved as time passed. Patients treated with exemestane plus ovarian suppression were affected by vaginal dryness and a greater loss of sexual interest that persisted over time. Although the spectrum of adverse events was different in the two treatment groups, changes in global quality-of-life indicators from baseline were similar[36].

The authors concluded that, compared with tamoxifen plus ovarian suppression, exemestane plus ovarian suppression significantly prolonged DFS in premenopausal women with endocrine-responsive early tumours. The evidence was stronger for very young women (<35 years of age) who had a higher risk of recurrence after adjuvant chemotherapy. However, the SOFT and TEXT trials required longer follow-up because the OS analysis was premature given the 5% risk of death[26,36,37].

AIs As Endocrine Therapy in Premenopausal Women With Advanced BCa

An AI combined with a GnRH analog has been studied in both first- and subsequent-line therapy in the advanced setting.

Carlson *et al.*[28] evaluated anastrozole plus goserelin in a prospective phase II trial, enrolling 35 premenopausal patients having HR+ metastatic or recurrent BCa. Of those patients, 3.1% achieved a complete response, and 34.4% achieved a partial response. The overall objective response rate was 37.5% (95% CI: 21% to 56%). Considering the 34.4% of women who experienced stable disease for at least 6 months, the overall clinical benefit rate was 71.9% (95% CI: 53% to 86%). Median time to progression was 8.3 months.

Similar results in first-line treatment were found in a nonrandomized study by Cheung *et al.*[29] using the same combination of anastrozole plus goserelin administered to 36 patients (median age: 44 years) with metastatic ($n = 28$) or locally advanced disease for 6 months or more (unless progression occurred beforehand). Some of the patients ($n = 13$) were subsequently treated with goserelin plus exemestane. In 24 patients (67%), some clinical benefit was achieved (5% complete response, 31% partial response, 31% stable disease for 6 months or more), with a median time to progression of 12 months and a duration of clinical benefit of 24 months.

Other trials explored the combination of letrozole and goserelin as first-line treatment. The phase II study conducted by Park *et al.*[30] evaluated the efficacy of letrozole plus goserelin compared with letrozole alone as first-line hormonal therapy in premenopausal and postmenopausal patients with metastatic BCa. The study included 73 patients; 35 were premenopausal, and 38 were postmenopausal. The two groups of women differed only by age and DFS (shorter in premenopausal patients). No differences were observed between the two groups in terms of clinical benefit (77% vs. 74%) or median time to progression (9.5 months vs. 8.9 months).

Liu *et al.*[32] focused on the efficacy of letrozole plus goserelin as first-line treatment in very young women affected by advanced BCa. In a selected group of 35 young women less than 35 years of age with a first diagnosis of advanced BCa, letrozole plus goserelin produced results similar to those in other studies. A 2.9% complete response rate and a 22.9% partial response rate (overall response rate: 25.7%) was observed. The clinical benefit rate was 65.7%. Median progression-free survival (PFS) was 9.6 months.

None of the aforementioned studies revealed an important toxicity caused by treatment with the combination of AI and goserelin. The Carlson study reported fatigue (50%), arthralgia (53%), and hot flashes (59%). Park and colleagues reported a significant reduction of bone mineral density in the premenopausal group who received combined therapy (13.3% vs. 17.4%; $p = 0.04$ at the lumbar spine), but that side effect could be prevented with the addition of bisphosphonate treatment.

Other trials have investigated AIs as second-line endocrine treatment for premenopausal women.

Forward *et al.*[27] evaluated anastrozole plus goserelin in patients with metastatic disease after first-line treatment with tamoxifen and goserelin. Of their patients, 75% achieved a clinical benefit, and 56% experienced stable disease (median duration of response: 17 months); 25% experienced progression before the end of 6 months.

Efficacy using the same combination and sequence was analyzed by Nishimura *et al.*[33] in a phase II trial that enrolled 37 premenopausal patients. The response rate was 18.9% (95% CI: 8.0% to 35.2%), the clinical benefit rate was 62.2% (95% CI: 44.8% to 77.5%), and the median PFS was 7.3 months.

Yao *et al.*[31] investigated letrozole plus goserelin in both the first- and second-line treatment of premenopausal patients with metastatic BCa. Their patients achieved a complete response rate of 3.8% and a partial response rate of 17.3%; 50% of patients achieved stable disease for more than 6 months, with a clinical benefit rate of 71.1%. The PFS was 10 months.

All studies investigating AI as second-line endocrine therapy reported good tolerance to treatment.

AIs in Premenopausal Women with BCa: Ongoing Clinical Trials

Currently, few studies are trying to evaluate the role of AIs in premenopausal patients with BCa. One is the COMPETE phase III randomized trial (see NCT02532400 at http://ClinicalTrials.gov), which is prospectively comparing the efficacy and safety of neoadjuvant AIs plus ovarian suppression with chemotherapy in premenopausal patients having HR+, HER2-negative BCa. Nowadays, neoadjuvant therapy is suggested for both early-stage and locally advanced BCa, which, compared with adjuvant therapy, is producing similar DFS and OS benefits. Complete responses achieved after neoadjuvant chemotherapy (compared with persistence of residual disease) are associated with superior outcomes. However, neoadjuvant chemotherapy in luminal HER2-negative BCa is not as effective as it is in other BCa subtypes.

The PERCHE phase III randomized trial (NCT00066807) is comparing the efficacy (DFS) of ovarian function suppression plus tamoxifen or exemestane with and without adjuvant chemotherapy in premenopausal women with resected HR+ BCa. The HOBOE phase III study (NCT00412022) is randomizing patients receiving triptorelin to tamoxifen, to letrozole, or to letrozole plus zoledronic acid. The aim of

version 1 of the study is to compare those three therapies with respect to patient bone loss. The study was amended in November 2009, and its extended version is comparing DFS in the three groups of premenopausal patients with early BCa.

The NCT00903162 phase II trial is testing the extended use of 2 years of letrozole plus leuprolide in premenopausal patients after treatment with tamoxifen for at least 4.5 years. Tolerance to 1 year of ovarian function suppression and letrozole is the primary outcome measure; secondary endpoints are bone mineral density and the incidence and severity of menopausal symptoms, musculoskeletal complaints, and overall quality of life.

The ER antagonist fulvestrant binds, blocks, and degrades ER; it has no agonist effects. Its efficacy and tolerability are comparable to those of third-generation AIs in patients with disease progression during prior tamoxifen therapy. Fulvestrant has been little studied in premenopausal women to this point. Several phase III clinical trials in postmenopausal women had already demonstrated the clinical effectiveness of fulvestrant as a treatment for advanced BCa at the standard dose of 250 mg monthly. However, evidence suggests that doubling the standard dose of fulvestrant results in major pharmacodynamic activity against the ER pathway and, compared with AIs, is associated with superior outcomes. Based on those observations, NCT01266213 (a randomized phase II trial) is comparing high-dose fulvestrant plus a LHRH agonist with AI plus a LHRH agonist or a LHRH alone in premenopausal patients with metastatic BCa after failure of tamoxifen. The study is still ongoing, with time to progression as its primary endpoint.

Palbociclib, a cyclin-dependent kinase 4/6 inhibitor associated with endocrine therapy, shows marked action in HR+ metastatic BCa in the postmenopausal setting. After a median of 16.5 months' follow-up, preliminary results from part 1 of a phase II trial suggested that palbociclib and letrozole are superior to letrozole alone and that the combination is associated with an improvement in the objective response and disease control rates (52% vs. 32% and 76% vs. 47% respectively). Those results suggest a benefit in premenopausal women. Most importantly, the recent PALOMA-3 trial revealed superior results from the addition of palbociclib to fulvestrant (median PFS: 9.2 months vs. 3.8 months; $p < 0.001$). Based on those background rationales, a phase II trial is ongoing to assess the safety and clinical antitumour activity of exemestane–goserelin–palbociclib compared with capecitabine in premenopausal patients with advanced HR+ BCa (NCT02592746).

The multicentre randomized double-blind placebo-controlled phase III MONALEESA-7 trial (NCT02278120) is evaluating the efficacy for PFS of LEE011, another inhibitor of cyclin-dependent kinase 4/6, combined with tamoxifen and goserelin or a nonsteroidal AI and goserelin in premenopausal women with advanced HR+ BCa.

DISCUSSION

Breast cancer is not a frequent clinical and psychosocial condition in young women, despite its increased incidence in premenopausal women in several countries. The biologic characteristics of BCa (HR status, HER2 amplification, proliferation, grade), tumour stage, and patient comorbidities should drive the choice of the best therapy in the early and advanced settings. Adjuvant endocrine treatment should be indicated in premenopausal patients with invasive HR+ BCa regardless of age, lymph node status, or use of chemotherapy. Given the results achieved in postmenopausal patients, AIs in combination with ovarian suppression have been tested in the adjuvant setting in premenopausal patients with early BCa. In the past, the only treatment of choice was tamoxifen alone or in combination with a LHRH analog.

The ABCSG (Austrian Breast and Colorectal Cancer Study Group)–12 trial has shown a comparable DFS for 3-year adjuvant therapy with anastrozole–goserelin and tamoxifen–goserelin[38]. However, the recent results of the SOFT and TEXT trials provided additional evidence about AIs as adjuvant treatment in premenopausal BCa patients. A combined analysis of the data from those two trials demonstrated that, compared with tamoxifen plus ovarian suppression, adjuvant endocrine therapy with exemestane plus ovarian suppression in premenopausal patients with HR+ BCa was associated with a significantly improved DFS and an extended disease-free interval and interval without distant recurrence.

The differing results emerging from ABCSG-12 and the TEXT and SOFT trials might be related to higher statistical power in the latter combined analysis (with 3 times the number of events) and varying treatment durations: the 3-year duration of AI therapy in ABCSG-12 might have been insufficient compared with 3 years of tamoxifen because the study manifested a carryover effect after treatment interruption.

Given the foregoing evidence, adjuvant treatment with ovarian suppression plus exemestane represents an important option, especially for very young women (<35 years of age) who have sufficient risk of recurrence to suggest adjuvant chemotherapy. However, follow-up in TEXT and SOFT is relatively short, and few data about long-term adverse events are available.

The choice of endocrine treatment should be based on patient comorbidities and the toxicity profiles of the various drugs: tamoxifen is associated with menopausal symptoms (hot flashes, sweats, weight gain, and sexual dysfunction), thromboembolic events, endometrial hyperplasia, and uterine tumours. Compared with tamoxifen plus ovarian suppression, exemestane plus ovarian suppression is associated with more frequent adverse sexual, musculoskeletal, and bone density events.

With respect to adjuvant endocrine treatment, it is also important to emphasize that, based on recent data, prolonged adjuvant AI therapy (5–10 years) is associated with a significant reduction in DFS events, but that the absolute difference is relatively small and that longer endocrine therapy results in a higher fracture rate[39]. That option is therefore more often proposed to women with a high risk of recurrence. Even in extended use, AIs must be given with a LHRH analog as long as the woman remains premenopausal. Despite recent advances in the study of ovarian suppression, several grey zones remain[40]. For example, what is the optimal extended approach in women treated

with 5 years of a LHRH analog plus an AI? And how is the onset of menopause to be evaluated during extended use?

Neoadjuvant endocrine therapy in premenopausal women has never been widely and adequately studied. As was mentioned before for early BCa, endocrine therapy should be chosen for HR+ disease even in the metastatic setting unless there is evidence of endocrine resistance or visceral crisis. In premenopausal patients with HR+ metastatic BCa, evidence, albeit derived from phase II trials, suggests an advantage of combining an AI with a LHRH analogue. Such a combination could therefore represent a possible option.

Given the efficacy of fulvestrant in postmenopausal women, that agent has also been studied in premenopausal women. Bartsch *et al.*[41] found a clinical benefit rate of 58% and a significantly better outcome with fulvestrant and goserelin in 26 women pretreated with tamoxifen and AI (each combined with goserelin).

No specific endocrine resistance mechanisms have been identified in young women, and all therapeutic strategies developed to reverse endocrine resistance have, until now, been applied only in postmenopausal patients.

Overweight represents a potential factor in endocrine resistance to hormonal therapy with AIs. The HR+ form of BCa often occurs in overweight women, and recent data demonstrate a negative effect of body mass index (BMI) on AI efficacy in postmenopausal women[42]. In particular, the ATAC study randomized 5172 postmenopausal women with early HR+ BCa to receive hormonal therapy with tamoxifen or the AI anastrozole. The study demonstrated a higher risk of local recurrence and metastasis in patients with a BMI exceeding 35, and treatment with anastrozole was associated with a higher risk of recurrence in women with a BMI exceeding 30. In contrast, the efficacy of tamoxifen was independent of BMI[43]. Whether, compared with their normal-weight counterparts, overweight premenopausal women receiving adjuvant AIs can experience the same benefit for reduced risk of recurrence is currently unclear. The data from ABCSG-12 seem to agree with those emerging from the ATAC study. The latter trial investigated the effect of BMI on the efficacy of endocrine therapy in the adjuvant setting in premenopausal women. Compared with women receiving tamoxifen, women with a BMI of 25 kg/m^2 or greater, treated with anastrozole, had a 50% higher risk of disease recurrence (95% CI: 0.93 to 2.38; $p = 0.08$) and a risk of death that was increased by a factor of 3 (95% CI: 1.35 to 6.82; $p = 0.004$)[44].

The efficacy of the combination of anastrozole and ovarian suppression in premenopausal patients seems to be significantly influenced by BMI, which might be caused by incomplete suppression of estrogen in serum[45–47] and the crosstalk between estrogen and the insulin and insulin-like growth factor signalling systems[44].

All of the foregoing data emerged from studies comparing tamoxifen with anastrozole, rather than with letrozole or exemestane or AIs in general. Some studies suggest that, after 2 years of adjuvant tamoxifen therapy, there is an advantage, in terms of body composition, in switching postmenopausal patients to exemestane treatment instead of continuing with adjuvant tamoxifen[48,49]. Important conclusions will be drawn from the distribution of patients according to BMI in both treatment groups in the combined analysis of SOFT and TEXT[50].

Finally, ongoing clinical trials will provide useful information about the use and the optimal duration of therapy with AIs and possible combinations with targeted therapies.

CONCLUSIONS

In recent years, several studies have indicated that AIs combined with a GnRH analog are safe and effective in premenopausal patients with HR+ BCa. However, the use of those agents should be individualized based on the biologic characteristics and stage of the disease, the patient's comorbidities, and not least, the individual's personal choice. All of the foregoing variables could drive the decision, not only about the type of hormonal therapy, but also about its duration. Thus, a multidisciplinary approach is fundamental both to optimize BCa cure and to minimize the effect of adverse events.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

*Clinica di Oncologia Medica e Centro Regionale di Genetica Oncologica, Università Politecnica delle Marche, Ancona, Italy.

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