Anti-Tumor Treatment

New insights on the role of luteinizing hormone releasing hormone agonists in premenopausal early breast cancer patients

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ABSTRACT

Luteinising hormone releasing hormone agonists (LH-RHa) are effective in the treatment of advanced endocrine-sensitive breast cancer in premenopausal patients, but their role in the adjuvant setting has remained controversial for a long time.

Tamoxifen for 5 years has been traditionally considered the standard endocrine therapy for premenopausal patients and this is still valid for many patients. However, the recently reported SOFT trial has suggested that adding ovarian function suppression (OFS) to tamoxifen could improve DFS in women at sufficient risk to warrant adjuvant chemotherapy and who remained premenopausal after this therapy. The administration of an aromatase inhibitor plus OFS represents an additional therapeutic option for hormone-receptor positive premenopausal breast cancer patients, according to the combined analysis of the SOFT and TEXT trials. Temporary ovarian suppression induced by LH-RHa has been recognized as an effective strategy to preserve ovarian function from the toxic effects of chemotherapy and is now recommended in young breast cancer patients with endocrine-insensitive tumors.

In this review, we discuss recent data on the role of LH-RHa in combination with tamoxifen or with an aromatase inhibitor, and we comment on its role as a strategy to preserve ovarian function in young patients candidates for adjuvant or neo-adjuvant chemotherapy.

Introduction

Approximately 11% of women with breast cancer are diagnosed before 45 years [1]. More than half of premenopausal breast cancer women have a tumor expressing hormone receptors [2] and are candidates for hormonal therapy. In breast cancer women younger than 45 years, tamoxifen for 5 years induces an absolute 15-year benefit of 10.6% in overall survival, reducing the 15-year breast cancer mortality from 35.9% to 25.3% (Relative Risk 0.71; 95% CI 0.61–0.83, p = 0.00002) [3] and it has been considered for a long time the standard adjuvant endocrine therapy for premenopausal patients.

Recent data from randomized studies showed that the absolute benefit of the adjuvant treatment with tamoxifen, in terms of breast cancer mortality reduction, can be improved by nearly 3% by extending its duration from 5 to 10 years [4,5]. Results from randomized studies reported in the last year and evaluating the role of the LH-RHa in addition to tamoxifen [6] or to aromatase inhibitors [7] and the role of this strategy in ovarian function preservation during chemotherapy [8] are expected to change current clinical practice for the adjuvant treatment of hormone-receptor positive premenopausal breast cancer women.

In this review, we discuss available data on (1) the role of LH-RHa in combination with tamoxifen; (2) the role of LH-RHa in combination with aromatase inhibitors; (3) the role of LH-RHa as a strategy to preserve ovarian function during chemotherapy.

LH-RHa and tamoxifen

Few trials addressed the effects of LH-RHa plus tamoxifen as compared with tamoxifen alone [6,9,10]. In the ZIPP study, 2710 patients were randomly assigned to four different arms: no treatment (476 patients); tamoxifen alone (879 patients); goserelin alone (469 patients); and the combination of tamoxifene and goserelin (882 patients) [9]. The three endocrine therapies were administered for 2 years. At a median follow-up of 12 years, each of the three hormonal therapies was associated with a reduction

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in the risk of both breast cancer recurrence and death from breast cancer. The effect of goserelin depended on whether women received tamoxifen. In women who did not receive tamoxifen, goserelin was associated with a 34% reduction in the risk of having an Disease Free Survival (DFS) event (defined by the occurrence of a recurrence, a new tumor or death) and a 29% reduction in risk of overall mortality (Table 1). In women who received tamoxifen, there was a much smaller, and statistically not significant, benefit due to goserelin: 9% reduction in risk of DFS events (hazard ratio [HR] = 0.91; 95% CI 0.77–1.07), and 2% reduction in risk of overall mortality (HR = 0.98; 95% CI 0.73–1.09). The main limitation of the study was the duration of the endocrine therapy for 2 years, which does not reflect current standard practice. The meta-analysis by Cuzick et al. [11] showed that the addition of an LH-RHa to tamoxifen was not associated with a significant reduction in the HR for recurrence (14.5% reduction, 95% CI 32.7–73.8% reduction to 8.6% increase, p = 0.33). On the basis of the above-reported evidence, in 2011 the American Society of Clinical Oncology (ASCO) experts recommended that ovarian function suppression (OFS) should not be routinely added to systemic therapy with chemotherapy, tamoxifen, or the combination of tamoxifen and chemotherapy, but they also stated that studies ongoing at that time would have had the potential to alter this recommendation [12]. Since the 2011 ASCO recommendations, the results of two additional phase III studies have been published [6,10]. In the small trial by Tevaarwerk et al. [10], 345 node-negative, premenopausal breast cancer women were enrolled: 171 received tamoxifen alone and 174 tamoxifen plus OFS. OFS was obtained by LH-RHa administration in 36% of study population, by bilateral oophorectomy in 42% and by bilateral ovarian irradiation in 13%. Nine percent of patients refused OFS. Adjuvant chemotherapy was not permitted. At a median follow up of 9.9 years, there was no difference between arms for DFS or overall survival (OS) (Table 1). OFS resulted in more menopausal symptoms and sexual dysfunction. Due to the small sample size, the study was underpowered to draw conclusions about the impact on DFS and OS when adding OFS to tamoxifen.

The Study of Ovarian Function Suppression and Tamoxifen (SOFT) [6] was a large, international trial in which 3066 premenopausal women, stratified according to prior receipt of chemotherapy, were randomly assigned to receive 5 years of tamoxifen (n = 1021), tamoxifen plus OFS (n = 1024), or exemestane plus OFS (n = 1021). OFS was achieved through administration of the LH-RHa triptorelin in 80.7% of patients. The primary analysis tested the hypothesis that tamoxifen plus OFS would improve DFS as compared with tamoxifen alone. At a median follow-up of 67 months, the 5-year DFS was 86.6% in the tamoxifen plus OFS and 84.7% in the tamoxifen group (HR: 0.83; 95% CI 0.66–1.04; p = 0.10) (Table 1). In the multivariable Cox proportional-hazards model, adjusted for prognostic factors, tamoxifen plus OFS significantly reduced the hazard of recurrence, a second invasive cancer, or death, as compared with tamoxifen alone (HR: 0.78; 95% CI 0.62–0.98; p = 0.03). Most recurrences and deaths were reported in patients who had received prior chemotherapy. In this subgroup of patients, which accounted for 53.3% of the overall study population, the 5-year DFS was 80.7% in the tamoxifen plus OFS group and 77.1% in the tamoxifen group (HR: 0.82; 95% CI 0.64–1.07), and the 5-year OS was 94.5% in the tamoxifen plus OFS group and 90.9% in the tamoxifen group (HR: 0.64; 95% CI 0.42–0.96). The Authors concluded that adding OFS to tamoxifen did not provide a significant benefit in the overall study population; however, for women at sufficient risk to warrant adjuvant chemotherapy and who remained premenopausal, the addition of OFS improved disease outcomes. A total of 233 patients younger than 35 years were

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Treatment arm</th>
<th>N patients</th>
<th>Median age</th>
<th>5-year DFS rate%</th>
<th>5-year OS rate%</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hackshaw et al. [9]</td>
<td>Phase III</td>
<td>Tam</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Toxicity</td>
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<tr>
<td></td>
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<td>Tam + LH-RHa</td>
<td>469</td>
<td>NR</td>
<td>84.7</td>
<td>95.1</td>
<td>Hot flushes, sweating, decreased libido, vaginal dryness, insomnia, depression more common in Tam + OFS group than in Tam alone group</td>
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<td>Phase III</td>
<td>Tam + OFS</td>
<td>174</td>
<td>NR</td>
<td>81.9</td>
<td>96.7</td>
<td></td>
</tr>
<tr>
<td>Francis et al. [6]</td>
<td>Phase III</td>
<td>Tam</td>
<td>NR</td>
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<td>Toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tam + OFS</td>
<td>1024</td>
<td>NR</td>
<td>84.7</td>
<td>96.6</td>
<td><em>(0.66–1.04)</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tam + LH-RHa</td>
<td>1021</td>
<td>NR</td>
<td>86.6</td>
<td>96.7</td>
<td><em>(0.66–1.04)</em></td>
</tr>
</tbody>
</table>

Abbreviations: C: chemotherapy; Tam: Tamoxifen; LHRHa: LH-RHa; LHR analogue; OFS: ovarian function suppression; Exe: exemestane; NR: not reported; DFS: disease free survival; OS: overall survival; HR: hazard ratio.
included in the primary analysis and 94.0% of them had received previous chemotherapy. Among these women, the 5-year freedom from breast cancer was 67.7% (95% CI 57.3–76.0) in the tamoxifen alone group, and 78.9% (95% CI 69.8–85.5) in the tamoxifen plus OFS. Grade 3 or higher adverse events were observed in 31.5% of the patients on tamoxifen plus OFS as compared with 23.7% of those on tamoxifen alone. Hot flushes, sweating, decreased libido, vaginal dryness, insomnia, depression, musculoskeletal symptoms, hypertension, and glucose intolerance were reported more frequently in the tamoxifen plus OFS group than in the tamoxifen alone group. Osteoporosis, defined by a T score of less than −2.5, was observed in 5.8% of patients on tamoxifen plus OFS and in 3.5% of those on tamoxifen alone.

Results from SOFT trial can be considered the most robust evidence available to date on the role of adding OFS to tamoxifen and suggest that OFS should be considered in high risk and in very young (less than 35 years) patients.

**LH-RHα and aromatase inhibitors**

Aromatase inhibitors are superior to tamoxifen in premenopausal breast cancer patients [13] and their role in premenopausal women receiving an LH-RHα has been partly clarified in the last few years. Until 2009, available data on the direct efficacy comparison between LH-RHα plus tamoxifen and LH-RHα plus an aromatase inhibitor came from a single study in which 1803 premenopausal hormone-receptor positive (HR+) breast cancer patients were randomized to receive goserelin plus tamoxifen or anastrozole, with or without zoledronic acid [14]. Nearly 70% of randomized patients had a node-negative disease and less than 10% received adjuvant chemotherapy. At a median follow-up of 3.9 years no significant difference in DFS between the anastrozole and tamoxifen groups was observed. A higher rate of distant metastases was observed in the anastrozole group than in the tamoxifen group. The updated analysis of this study at a median follow-up of 7.9 years confirmed that there was no difference in DFS between patients receiving anastrozole and tamoxifen (anastrozole vs tamoxifen, HR: 1.13; 95% CI 0.88–1.45; p = 0.335), but those on anastrozole had shorter survival (HR: 1.63; 95% CI 1.05–1.45; p = 0.03) (Table 2) [15]. Main limitations of this study was the shorter than standard duration of the endocrine therapy (3 years instead of 5 years).

The most important evidence on the role of aromatase inhibitors plus OFS in the adjuvant treatment of premenopausal breast cancer patients, come from the study of Pagani et al. which reported the results of a combined analysis on 4690 patients enrolled in two phase 3 trials [7]. In the two studies, premenopausal HR+ breast cancer patients were randomly assigned to receive exemestane plus OFS or tamoxifen plus OFS for 5 years. Chemotherapy was administered to 57.4% of the study population. At a median follow up of 5.7 years, the 5-year DFS was 91.1% in the exemestane plus OFS group and 87.3% in the tamoxifen plus OFS group (HR: 0.72; 95% CI 0.60–0.85; p < 0.001). Overall survival did not differ significantly between the two groups (HR: 1.14; 95% CI 0.86–1.51; p = 0.37) (Table 2). The Authors concluded that in premenopausal HR+ early breast cancer patients, adjuvant treatment with exemestane plus OFS, as compared with tamoxifen plus OFS, significantly reduced recurrence. The analysis of the patient-reported outcomes showed that patients on tamoxifen plus OFS were more affected by hot flushes and sweats than those on exemestane plus OFS. Patients on exemestane plus OFS reported more vaginal dryness, an increase in bone or joint pain, and greater loss of sexual interest. Changes in global quality of life indicators from baseline were similar between treatments [16].

The main limitation of the study of Pagani et al. remains its short follow up. The risk of relapse in HR+ patients is substantial

**Table 2**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Treatment arm</th>
<th>N patients</th>
<th>Median age</th>
<th>5-year DFS rate</th>
<th>5-year OS rate</th>
<th>DFS HR (95% CI)</th>
<th>OS HR (95% CI)</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gnant et al. [15]</td>
<td>Phase III</td>
<td>Anastrozole + LH-RHa ± Zol</td>
<td>903</td>
<td>45.5</td>
<td>NR</td>
<td>NR</td>
<td>1.13 (0.88–1.45)</td>
<td>1.63 (1.05–1.45)</td>
<td>No significant difference between the two group</td>
</tr>
<tr>
<td>Tam + LH-RHa ± Zol</td>
<td>900</td>
<td>45.4</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Pagani et al. [7]</td>
<td>Combined analysis of two phase III studies</td>
<td>Exemestane + LH-RHa</td>
<td>2359</td>
<td>43</td>
<td>91.1</td>
<td>95.9</td>
<td>0.72 (0.60–0.85)</td>
<td>1.14 (0.86–1.51)</td>
<td>Bone joint pain, vaginal dryness more common in Exe group, hot flushes, vaginal discharge more common in Tam group</td>
</tr>
<tr>
<td>Tam + LH-RHa</td>
<td>2358</td>
<td>87.3</td>
<td>96.9</td>
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</table>

Abbreviations: LH-RHa: LHRH analogs; Tam: tamoxifene; AI: aromatase inhibitor; Exe: exemestane; Zol. Ac.: zoledronic acid; NR: not reported; DFS: disease free survival; OS overall survival.
<table>
<thead>
<tr>
<th>Author</th>
<th>Primary end point</th>
<th>Treatment arm</th>
<th>No. patients</th>
<th>Median age</th>
<th>No. patients with hormone receptor positive/negative tumors</th>
<th>Pregnancies</th>
<th>POF rate (%)</th>
<th>p Value</th>
<th>Use of endocrine therapy</th>
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<td>Li M et al. [21]</td>
<td>Resumption of menses</td>
<td>CT</td>
<td>32</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>CT + LHRHa</td>
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<td>Badawy et al. [22]</td>
<td>No resumption of menses and ovulation at 8 months</td>
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<td>CT + LHRHa</td>
<td>39</td>
<td>30</td>
<td>NR</td>
<td>NR</td>
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<td>Sverrisdottir et al. [23]</td>
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<td>Control</td>
<td>63</td>
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<td>NR</td>
<td>90</td>
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<td></td>
<td></td>
<td>Tam</td>
<td>60</td>
<td>45</td>
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<td></td>
<td></td>
<td>LHRHa + Tam</td>
<td>64</td>
<td>45</td>
<td>45/21</td>
<td>NR</td>
<td>NR</td>
<td>93</td>
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<td></td>
<td></td>
<td>LHRHa</td>
<td>63</td>
<td>45</td>
<td>45/12</td>
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<td>CT</td>
<td>133</td>
<td>39</td>
<td>109/22</td>
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<td>25.9</td>
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<td></td>
<td></td>
<td>CT + LHRHa</td>
<td>148</td>
<td>39</td>
<td>117/29</td>
<td>3</td>
<td>8.9</td>
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<td>Gerber et al. [25]</td>
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<td>CT</td>
<td>30</td>
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<td>38.5</td>
<td>0/30</td>
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<td>NR</td>
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<td>39</td>
<td>20/7</td>
<td>0</td>
<td>12</td>
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<td>Elgindy et al. [28]</td>
<td>Resumption of menses at 12 months</td>
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<td>50</td>
<td>32.5</td>
<td>0/50</td>
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<td>48</td>
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<td>Postmenopausal levels of FSH and E2 in the absence of menstrual activity at 12 months</td>
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<td>42</td>
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<td>Li JW et al. [31]</td>
<td>Amenorrhea for the prior 12 months and postmenopausal levels of FSH at 12 months</td>
<td>CT → LHRHa</td>
<td>108</td>
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<td>0/108</td>
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<td>CT + LHRHa</td>
<td>108</td>
<td>37.5</td>
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<td>37.6</td>
<td>0/126</td>
<td>18</td>
<td>8</td>
<td></td>
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</table>

**Abbreviations:** CT: chemotherapy; LHRHA: LHRH analogs; NR: not reported; POF: premature ovarian failure.
after the fifth year after surgery [17]. This timing of recurrence sug-
gests that a long follow up in necessary to observe the true benefit
(or harm) of adjuvant treatment with aromatase inhibitors in
hormone-receptor-positive patients.

Despite this major limitation, the results of the study from
Pagani et al. suggest that an aromatase inhibitor plus OFS re-
resents an additional therapeutic option for HR+ premenopausal
breast cancer patients. However, when the treatment with an
aromatase inhibitor plus OFS obtained by LH-RHa is administered to
very young patients, clinicians should be aware that in a small
number of these patients the LH-RHa treatment may not induce
complete suppression of ovarian function [18,19]. In these patients,
treatment with an aromatase inhibitor can stimulate the residual
ovarian function leading to an increase instead of a decrease in
serum levels of estrogen; this should be monitored to rule out such
a potential stimulatory activity of the aromatase inhibitor. Ongoing
studies, such as the HOBOE trial (NCT00412022), are expected to
give new insights on the role of the treatment with an aromatase
inhibitor plus OFS in premenopausal breast cancer patients.

LH-RHa and preservation of ovarian function

Ovarian toxicity is a major side effect of chemotherapy in young
cancer patients. Chemotherapy-induced premature ovarian failure
(POF) has major consequences, including vasomotor symptoms,
increased risk of cardiovascular disease, sexual dysfunction, and
infertility [20]. Temporary ovarian suppression with LH-RHa duri-
gen chemotherapy is a potential strategy to preserve ovarian func-
tion. Several randomized studies evaluating the effect of LH-RHa
on chemotherapy-induced POF have been published [8,21–31]
(Table 3) and a meta-analysis including nine of these studies
showed a statistically significant reduction in the risk of POF
(OR = 0.43; 95% CI 0.22–0.84; p = 0.013) in patients receiving
LH-RHa [32]. Despite this result, the administration of an LH-RHa
during chemotherapy was until recently still considered an
experimental strategy for the preservation of ovarian function
and fertility, mainly due to the lack of data on long-term ovarian
function and pregnancy rate [33,34]. In 2014, the publication of
the results from two major phase III trials did fill this gap. In the
POEMS trial, 257 premenopausal women with hormone-receptor
negative breast cancer were randomly assigned to receive standard
chemotherapy plus an LH-RHa or standard chemotherapy without
LH-RHa. The ovarian failure rate was 8% in the LH-RHa group and
22% in the chemotherapy alone group (OR = 0.36; 95% CI 0.09–
0.97; p = 0.04) and pregnancy occurred in more women in the
LH-RHa group than in the chemotherapy alone group (21% vs
11%; OR = 2.45; 95% CI 1.09–5.51 p = 0.03) [8]. Therapy with gosere-
lin did not have a negative impact on survival: in fact, patients
who withdrew from the drug had improved DFS (p = 0.04) and
OS (p = 0.05) when compared with the control group. The updated
analyses [35], with a median follow up of 7.3 years of the Promise
study confirmed the higher, although statistical significance was
not reached, pregnancy rate in women treated with chemotherapy
plus LH-RHa as compared with women treated with chemotherapy
alone (2.9% vs 1.6%; HR: 2.56; 0.68–9.60, p = 0.142).

On the basis of these new data, the temporary ovarian
suppression with an LH-RHa is now recommended as a strategy
to preserve ovarian function in young breast cancer patients with
endocrine-insensitive tumors [36,37].

Conflict of interest statement

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