Cancer Treatment Reviews 42 (2016) 18–23

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumor Treatment

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

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ARTICLE INFO

Article history:
Received 6 October 2015
Received in revised form 10 November 2015
Accepted 13 November 2015

Keywords:
Breast cancer
LH-RH agonists
Endocrine therapy
Infertility
Ovarian ablation
Aromatase inhibitor

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-ha 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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http://dx.doi.org/10.1016/j.ctrv.2015.11.002
0305-7372/

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% reduction to 8.6% increase, $p = 0.20$) and death (15.9%, 40.7% reduction to 19.4% 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) (Table1). 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 1
Tamoxifen + LH-RHa versus tamoxifen.

Author	Study design	Treatment arm	N° patients	Median age	5-year DFS rate%	5-year OS rate%	DFS HR (95% CI)	OS HR (95% CI)	Toxicity
Hackshaw et al. [9]	Phase III	Tam	879	NR	NR	NR	0.69* (0.57–0.83)	0.72* (0.58–0.90)	Hot flushes most common in Tam + LH-RHa (44%) than in LH-RHa alone (26%) or in Tam alone (17%) groups
		LH-RHa	469	NR	NR	NR	0.66* (0.53–0.81)	0.71* (0.55–0.92)	
		Tam + LH-RHa	882	NR	NR	NR	0.63* (0.52–0.76)	0.64* (0.51–0.81)	
Tevaarwerk et al. [10]	Phase III	Tam	171	46	89.7	97.6	0.85** (0.47–1.6)	0.84** (0.37–2.0)	Hot flushes, weight gain, anxiety, depression more common in Tam + LHRHa group than in Tam alone group (22.4% vs 12.3% $p = 0.004$)
		Tam + OFS	174	44	87.9	95.2			
Francis et al. [6]	Phase III	Tam	1021	NR	84.7	95.1	0.83** (0.66–1.04)	0.74** (0.51–1.09)	Hot flushes, sweating, decreased libido, vaginal dryness, insomnia, depression more common in Tam + OFS group than in Tam alone group
		Tam + OFS	1024	NR	86.6	96.7			

Abbreviations: CT: chemotherapy; Tam: Tamoxifene; LHRHa: LHRH analogs; OFS: ovarian function suppression; Exe: exemestane; NR: not reported; DFS: disease free survival; OS: overall survival; HR: hazard ratio.

* Compared to no endocrine therapy.

** Tamoxifen + OFS compared with tamoxifen alone.