Efficacy of a quarterly versus monthly formulations of human of luteinizing hormone-releasing hormone agonists in inducing ovarian suppression during adjuvant treatment of hormone receptor-positive localized breast cancer in premenopausal women – a retrospective real-life study.

Dias Deborah[2]; Leite Luciana[1]; Lima Vladmir[1]; Sanches Solange [2]
[1] AC Camargo Cancer Center [2] Oncologia D'OR

Introduction

Premenopausal women with hormone receptor positive (HR+) early breast cancer (BC) who receive chemotherapy have significant reduced risk of distant relapse when treated with ovarian function suppression (OFS) and aromatase inhibitors (AI) in the adjuvant setting. Clinical trials supporting this practice used predominantly monthly luteinizing hormone-releasing hormone agonists (LHRHa) formulations. However, due to the convenience of dosing, other formulations are frequently used in clinical practice. The aim of this study is to compare the efficacy of quarterly LHRHa dosing with monthly LHRHa dosing in inducing OFS in premenopausal HR+ patients undergoing adjuvant AI plus LHRHa.

Methods and Materials

Study design: Retrospective, single-center, cohort, real-world study.
Population: Pre/perimenopausal HR+ (HER2+or-) early BC patients treated with AI plus LHRHa between 2015 and 2021.
Intervention: Subcutaneous injection of goserelin 10.8 mg once every 3 months (quarterly formulation) or goserelin 3.6 mg once every month (monthly formulation).

Primary Outcome: Ovarian suppression failure (OSF) - a composite outcome defined by one of the following criteria:

- E2 levels above the postmenopausal range (according to local laboratories references);
- Menstrual bleeding during treatment;
- Switch AI to tamoxifen due medical judgement of castration failure
- Need for salpingophorectomy due to OSF.
- For patients receiving the quarterly LHRHa, the need to switch to the monthly formulation as per medical judgement due to castration failure was also considered OSF.

Secondary outcomes:

- Compare the impact of both LHRHa on relapse free survival (RFS) and overall survival (OS), as well as the impact of OSF on survival outcomes.

Statistical comparisons included Fisher's Exact test, Chi-square, Mann- Whitney, Kaplan-Meier, and regression analyses. The significance level was set at 5%.

Figure 1. Flow Diagram

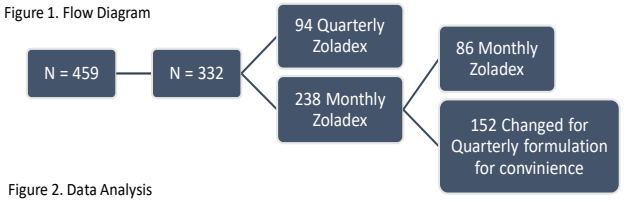


Figure 2. Data Analysis

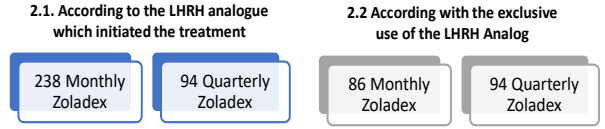


Table 1: OSF according to LHRH analog which initiated treatment.

		Monthly (238) (%)	Quarterly (94) (%)	Sig	Total
OSF	**Yes**	7 (2,9)	20 (21,3)	< 0,001	27 (8,1%)
E2 levels above the postmenopausal range	**Yes**	8 (3,4)	5 (5,3)	0,53	13 (3,9%)
Menstrual Bleeding	**Yes**	4 (1,7)	6 (6,4)	0,034	10 (3%)
Switch AI to TMX due to castration failure	**Yes**	6 (2,5)	3 (3,2)	0,717	9 (2,7%)
Swicth to Monthly Treatment due to castration failure	**Yes**	0	17 (18,1)		17
	Not evaluated	238	0		238
Need for Salpingophorectomy	**Yes**	1 (0,4)	1 (1,1)	0,487	2 (0,6%)
Duration of treatment	**Mediana**	17 m (1 -71)	55 m (3 – 83)	< 0,01	

Results

Among 332 patients, 238 received monthly LHRHa and 94 patients received quarterly LHRHa. Baseline clinical characteristic were balanced between the two groups, except for the duration of treatment, which was longer in the quarterly versus the monthly LHRHa group (55 months x 17 months, p < 0.01). This imbalance in the duration of treatment occurred because 152 patients in the monthly LHRHa group changed to quarterly LHRHa administration after some time, due to patient convenience. OSF occurred in 27 patients, 20/94 (21.3%) in quarterly LHRHa vs. 7/238 (2.9%) in monthly LHRHa (p < 0.01). A sensitivity analysis was performed to adjust for the duration of treatment, excluding patients in the monthly group who changed to quarterly administration. In this analysis 180 patients were included, 86 in the monthly LHRHa and 94 in the quarterly LHRHa group. OSF still was higher in the quarterly vs. monthly group (21.3% x 2.3%). Considering the entire population the median follow-up of 59 months, 18 patients (5.4%) had disease recurrence (4 local/14 distant) and 7 patients died, with no diference between initial choice of LHRHa formulation (HR 0.65 95%CI 0.23 – 1.82). On uni and multivariate analysis of RFS, age, cT, cN+, HER2 status and histologic grade were not significant factors, and only OSF remained significant in a model including clinical stage and type of analogue (HR 5.11 95%CI 1.54 – 17, p= 0.008). OS was also not impacted by initial type of LHRHa used (HR 0.20 95%CI 0.02 – 1.71, p=0.14), but further analysis were limited by the number of events.

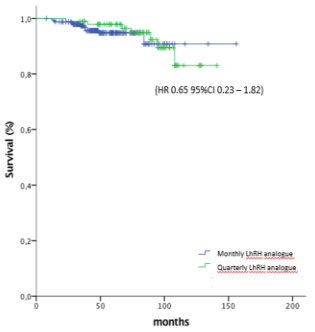
Table 2. Univariate analysis of clinicopathological characteristics with Relapse Free Survival (RFS)

Variable	Univariate	p
Age ≤ 35	0.93 (0.33 – 2.62)	0.88
Tumor Size		
T1 ou T2	1	0.82
T3 ou T4	0.89 (0.31 – 2.51)	
Positive Lynphnode	1.55 (0.55 – 4.36)	0.41
Staging		
I	1	
II	1.04 (0.27 – 4.01)	0.96
III	1.37 (0.36 – 5.21)	0.64
Histologic Grade		
I e II	1	0.76
III	0.87 (0.32 – 2.32)	
Subtipe		
Luminal	1	0.62
Luminal HER2 positive	0.76 (0.25 – 2.31)	
Chemotherapy Use	0.83 (0.11 – 6.33)	0.86
LHRH analog which initiated treatment		
Monthly	1	0.41
Quarterly	0.65 (0.23 – 1.82)	

Table 3: RFS - Uni e Multivariate Analysis

Variable	Multivariate	p
Staging		
I e II	1	0.40
III	1.52 (0.60– 3.88)	
OSF	**5.11 (1.54 – 17)**	**0.008**
LHRH analog which initiated treatment		
Monthly	1	0.18
Quarterly	0.45 (0.14 – 1.44)	

Figure 3. Relapse Free Survival



Conclusions

The use of the quarterly dosage of the LHRH analogue was linked to higher ovarian suppression failure, biased by the longer treatment duration of this formulation in our sample. OSF was an important prognostic factor for RFS and estradiol levels should be monitored. Prospective studies are needed to clarify doubts regarding the efficacy of quarterly LHRH analogues.

Contact

Deborah Cathlá Ribeiro Dias
Oncologia D'OR
cathaladeborah@gmail.com

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