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JOURNAL OF CANCEROLOGY REVIEW ARTICLE

Exemestane improves overall survival, compared with anastrozole, in postmenopausal patients with metastatic breast cancer

RODRIGO ADAME-MORENO*, DENISE ACUÑA-GONZÁLEZ AND YESSICA PACHECO-VALLEJO

Department of Oncology Surgery, Instituto Nacional de Cancerología, Mexico City, Mexico

ABSTRACT

Introduction: Aromatase inhibitors (AIs) (anastrozole, letrozole, and exemestane) are the treatment of choice in patients with advanced-stage breast cancer and positive hormone receptors. They have shown superiority over tamoxifen as the first-line therapy in terms of response, particularly in time to progression. Presumably, anastrozole and letrozole are slightly superior to tamoxifen as the first-line therapy for postmenopausal patients with metastatic breast cancer. **Materials and Methods:** A review of the literature was undertaken using the words AIs, metastatic breast cancer as MeSH descriptors in browsers with evidence of clinical practice guidelines. Systematic revisions and randomized clinical trials retrieved from PubMed, Cochrane, ESMO Clinical Practice Guideline, NICE Guidelines, and Trip database were analyzed. A total of 11 articles met the inclusion criteria. **Results:** Exemestane was correlated to response rates (36.2%, 95% confidence interval [CI], 18.5-45.9%) and complete response (6.4%). Anastrozole had a response rate of 46%, 95% CI, 32.2-59.8% and a complete response of 14%. The clinical benefit was 59.6% and 68% in exemestane and anastrozole, respectively. The median disease-free interval (DFI) was 6.1 months (95% CI, 2.5-9.6 months) for patients who received exemestane and 12.1 months (95% CI, 7.3-16.8 months) for the patients receiving anastrozole. **Discussion:** Endocrine therapy is a feasible method to palliate patients with metastatic breast cancer. AIs are the election treatment in postmenopausal patients because of the improvement they achieve in DFI. **Conclusion:** As a rule, letrozole and exemestane are the best drugs due to their response rates (without significant differences in overall survival or DFI), compared with anastrozole.

Key words: Aromatase inhibitors. Breast cancer. Metastatic breast cancer. Postmenopause.

Correspondence author:
*Rodrigo Adame-Moreno
E-mail: rodrigoadame@gmail.com

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RESUMEN

Introducción: Los inhibidores de la aromatasa (anastrozol, letrozol, exemestano) son el tratamiento elegido en pacientes con cáncer de mama en etapa avanzada y receptores hormonales positivos. Han demostrado superioridad sobre el tamoxifeno como terapia de primera línea en términos de respuesta, particularmente en tiempo de progresión. Presumiblemente, el anastrozol y el letrozol son ligeramente superiores al tamoxifeno como tratamiento de primera línea para pacientes posmenopáusicas con cáncer de mama metastásico. **Material y métodos:** Se realizó una revisión de la literatura utilizando los términos «inhibidores de aromatasa» y «cáncer de mama metastásico» como descriptores MeSH en navegadores con evidencia de guías de práctica clínica. Se analizaron las revisiones sistemáticas y los ensayos clínicos aleatorizados obtenidos de PubMed, Cochrane, la Guía de práctica clínica de la *European Society for Medical Oncology* (ESMO), las Directrices del *National Institute for Health and Clinical Excellence* (NICE) y Tripdatabase. Un total de 11 artículos cumplieron los criterios de inclusión. **Resultados:** El exemestano se correlacionó con las tasas de respuesta (36.2%; intervalo de confianza [IC] 95%: 18.5-45.9%), respuesta completa (6.4%). El anastrozol tuvo una tasa de respuesta del 46% (IC 95%: 32.2-59.8%) y una respuesta completa del 14%. El beneficio clínico fue del 59.6 y 68% en exemestano y anastrozol, respectivamente. La mediana del intervalo libre de enfermedad (IFD) fue de 6.1 meses (IC 95%: 2.5-9.6 meses) para las pacientes que recibieron exemestano y 12,1 meses (IC 95%: 7.3-16.8 meses) para las pacientes tratadas con anastrozol. **Discusión:** La terapia endocrina es un método factible para paliar a las pacientes con cáncer de mama metastásico. Los inhibidores de aromatasa son el tratamiento de elección en pacientes posmenopáusicas debido a la mejora que logran en el IFD. **Conclusiones:** Como regla general, el letrozol y el exemestano son los mejores medicamentos debido a sus tasas de respuesta (sin diferencias significativas en la supervivencia global o el IFD), en comparación con el anastrozol. (J CANCEROL. 2018;5:58-64)

Corresponding author: Rodrigo Adame-Moreno, rodrigoadame@gmail.com

Palabras clave: Inhibidores de la aromatasa. Cáncer de mama. Cáncer de mama metastásico. Posmenopausia.

INTRODUCTION

In spite of the high breast cancer incidence, clinical outcomes have improved steadily over the past 20 years, which has significantly decreased mortality rate.

Characteristics of the tumor biology are heterogeneous, but up to 75% of breast cancers expresses estrogen receptors and are potentially sensitive to endocrine management, which reduces the proliferative estrogenic stimulus[1]. In the mid-1990s, a new class of hormone oral agents was available, that is, the third generation of aromatase inhibitors (AIs) for postmenopausal patients with metastatic breast cancer[2].

These agents were developed after identifying P450 cytochrome and are classified into two categories: (1) reversible inhibitors (anastrozole and letrozole) and (2) the irreversible inhibitor, exemestane[3]. Exemestane-induced suppression is similar to the one induced by letrozole, and slightly superior to the anastrozole-induced suppression[4] due to a higher reduction in estrogen levels and

reversal of the adaptive hypersensitivity mechanism. Furthermore, exemestane androgenic activity may induce a second antitumor effect[5].

Objective

Since there are just a few trials showing effect of endocrine or sequential therapy in survival of patients with metastatic breast cancer, the authors of this document conducted a review of the literature to determine the activity and tolerance to exemestane and anastrozole as the first-line treatment for postmenopausal patients with metastatic breast cancer.

Hypothesis

Exemestane, in the metastatic breast cancer setting, prolongs overall survival (OS), compared with anastrozole.

EVIDENCE

In early-stage breast cancer, adjuvant tamoxifen (20 mg for 2 or 3 years), followed by exemestane (25 mg/day, up to 5 years) or anastrozole (1 mg daily up to 5 years) is an alternative to 5-year therapy with tamoxifen with similar disease-free interval (DFI) and OS[6]. However, in patients with advanced-stage breast cancer, AIs (anastrozole, letrozole, and exemestane) are the best option because they have shown superiority over tamoxifen as the first line in terms of response, especially in time to progression. There is no preference for one over another of these AIs, but nonsteroidal AIs should be administered after steroidal AIs progression and *vice versa*[7].

Phase III clinical trials suggest that anastrozole and letrozole are slightly superior to tamoxifen as the first-line therapy for postmenopausal patients with metastatic breast cancer[2].

AIs have been directly compared to tamoxifen as the first-line treatment for postmenopausal women with metastatic breast cancer. All of the AIs have proved benefits in this setting, but results have been more consistent for letrozole regarding time to progression, compared to tamoxifen[3]. Anastrozole and letrozole safety profiles were similar, and the most common side effects reported in both arms were bone pain (13% vs. 15%, respectively), dyspnea (11% vs. 10%), and nausea (11% vs. 8%)[3].

A randomized clinical trial, comparing anastrozole versus exemestane, enrolled 130 patients and 128 patients (64 anastrozole and 64 exemestane) were included in the intention-to-treat analysis. The clinical benefit in visceral sites was 32% in the patients treated with anastrozole and 38% in patients under exemestane treatment. The median survival was 33.3 months and 30.5 months in anastrozole and exemestane arms, respectively; however, treatment-related adverse events were more frequent with anastrozole (41%) than with exemestane (31%). Toxicities were consistent with previous reports, but the treatment-related adverse events were more frequent with anastrozole (41%) than with exemestane (31%). Overall, both approaches were well tolerated by postmenopausal patients with breast cancer and visceral metastases[5].

Current recommendations to treat metastatic breast cancer (with positive hormone receptors and negative HER) focus on hormone therapy. The drug chosen for the first-line treatment depends on the drug used as adjuvant in the upfront treatment; it may be an AI, tamoxifen, or fulvestrant. The combination of nonsteroidal AI and fulvestrant as the first-line therapy in postmenopausal patients prolonged DFI and OS, compared with just one AI in a Phase III clinical trial; however, in a second clinical trial did not show improvement. In a more detailed analysis, the benefit was limited to patients who had not been exposed to tamoxifen; thus, this types of patients benefit from a combination of AIs in metastatic breast cancer[8].

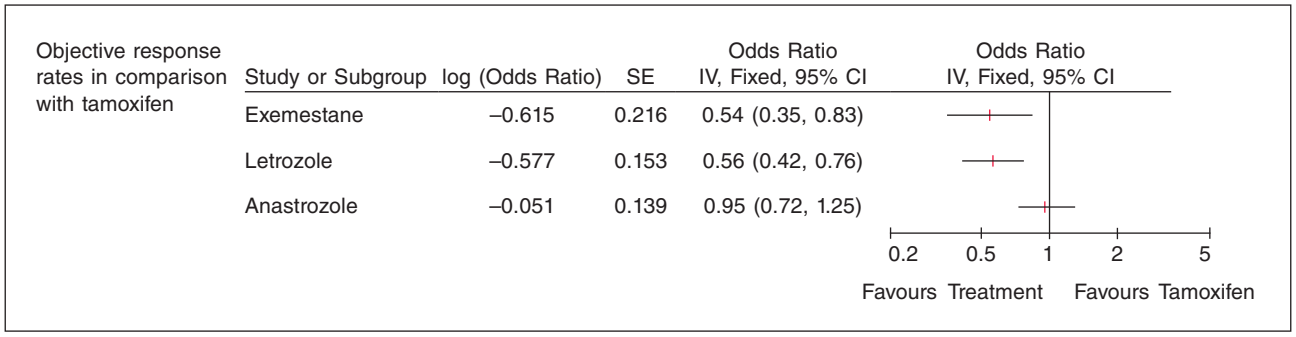


Figure 1. Objective response rates in comparison with tamoxifen *(source: Riemsma, et al.[9]).*

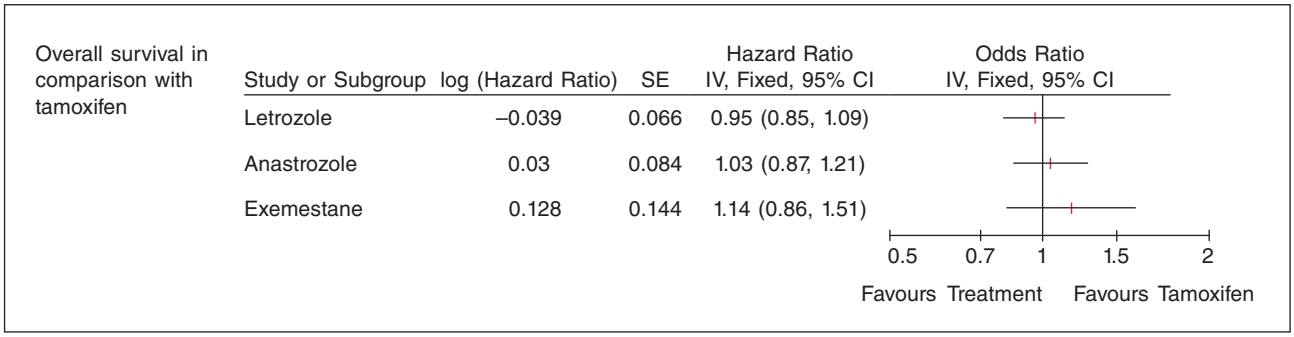


Figure 2. Overall survival in comparison with tamoxifen *(source: Riemsma, et al.[9]).*

In the systematic revision conducted by Riemsra et al., administration of exemestane, letrozole, and anastrozole was analyzed in patients with metastatic hormone-sensitive breast cancer, positive or negative HER, who had not been exposed to any other treatments. Four trials were included and the results were the following: (1) letrozole was superior to tamoxifen in terms of disease progression, objective response, and toxicity; (2) exemestane was superior to tamoxifen in terms of objective response; (3) anastrozole was significantly superior to tamoxifen in DFI; and (4) in comparison with AIs, exemestane and letrozole had a better objective response than anastrozole; however, there were no differences in OS and DFI. Evidently, it should be borne in mind that these results are based on indirect comparisons (Figs. 1 and 2, Table 1).

In another randomized, open-label, Phase II trial, exemestane and anastrozole were directly compared in patients with advanced disease. Patients received either exemestane 25 mg or anastrozole 2 mg orally once daily until disease progression. No other targeted therapies were administered. Randomization was conducted and patients were classified according to the Pocock and Simon algorithm to obtain three prognoses.

Table 1. Results in progression-free survival or time to progression (treatment vs. comparator)

Treatment	Comparator		
	Tamoxifen	**Letrozole**	**Anastrozole**
Letrozole	**0.70* (0.60-0.82)**		
Anastrozole	0.85* (0.71, 1.01)	1.22 (0.96, 1.54)	
Exemestane	0.87* (0.70, 1.08)	1.24 (0.95, 1.62)	1.02 (0.79, 1.35)

Values in bold represent significant difference in terms of overall survival; hazard ratio <1 indicates greater likelihood of better response on treatment versus comprator.
*Head-to-head comparison.
Source: Riemsma, et al.[9]

Factors were locally advanced or metastatic disease, treatment with adjuvant tamoxifen (yes or no), and chemotherapy for metastatic disease (yes or no). The primary endpoint was objective response rate. The secondary assessment criteria included clinical benefit, time to progression, OS, and toxicity. Between September 2001 and May 2003, 103 patients with positive estrogen and progesterone receptors and advanced or metastatic breast cancer were included in the study. They were randomized (51 patients received exemestane and 52 anastrozole) in 13 Spanish centers; 17 patients in the exemestane arm achieved response (36.2%, 95% CI, 18.5-45.9%), including three with complete response (6.4%). There were 23 responses in the anastrozole group (46%, 95% CI, 32.2-59.8%), including seven complete responses (14%). The clinical benefit was 59.6% and 68% in exemestane and anastrozole, respectively. In DFI, the median was 6.1 months (95% CI, 2.5-9.6 months) for patients receiving exemestane and 12.1 months (95% CI, 7.3-16.8 months) for the patients under anastrozole treatment. In the final analysis, 57 patients had died. The OS median was 48.3 months (95% CI, 18.3-78.3 months) for the patients who received anastrozole and 19.9 months (95% CI, 15.32-24.46 months) for the patients under exemestane treatment (Table 2, Figs. 3 and 4)[4].

It is worth noting that the current trial is the first one in reporting numeric differences in the activity between two of the third-generation AIs. Nonetheless, in an exploratory analysis, exemestane seemed to be more effective than anastrozole[4].

Table 2. Results of response and clinical benefit with the first-line aromatase inhibitor therapy

Response	No. of Patients (%)*	
	Exemestane Arm, n = 47	Anastrozole Arm, n = 50
CR	3 (6.4)	7 (14)
PR	14 (29.8)	16 (32)
ORR	17 (36.2)	23 (46)
95% CI	18.5-45.9	32.2-59.8
SD	9 (19.1)	11 (22)
Clinical benefit	28 (59.6)	34 (68)
PD	21 (44.7)	16 (32)

CR: complete response; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease.
*Note that there were 6 nonevaluable patients, including 4 patients in the exemestane arm and 2 patients in the anastrozole arm, who were not considered in this table.
Source: Llombart-Cussac, et al.[4]

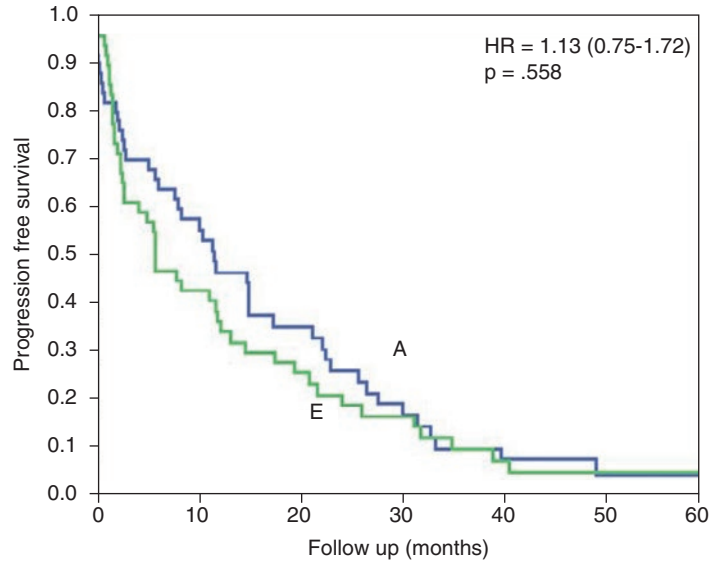
DISCUSSION

Not all the ER-positive tumors are sensitive to endocrine management; their sensitivity is variable in terms of decrease in tumor size and duration of the treatment effect. Therefore, before the resistance appears, endocrine therapy in advanced disease provides palliation, but not cure. Besides tumor regression, endocrine therapy may simply inhibit or decrease tumor growth; likewise, it may diminish the emergence of new symptoms and preserve quality of life[4].

There are a few trials showing effectiveness when comparing two AIs. Most of the evidence is focused on comparing one of these versus tamoxifen; however, AIs are the treatment of choice in patients with advanced breast cancer because they have proved superiority as the first line in DFI[7].

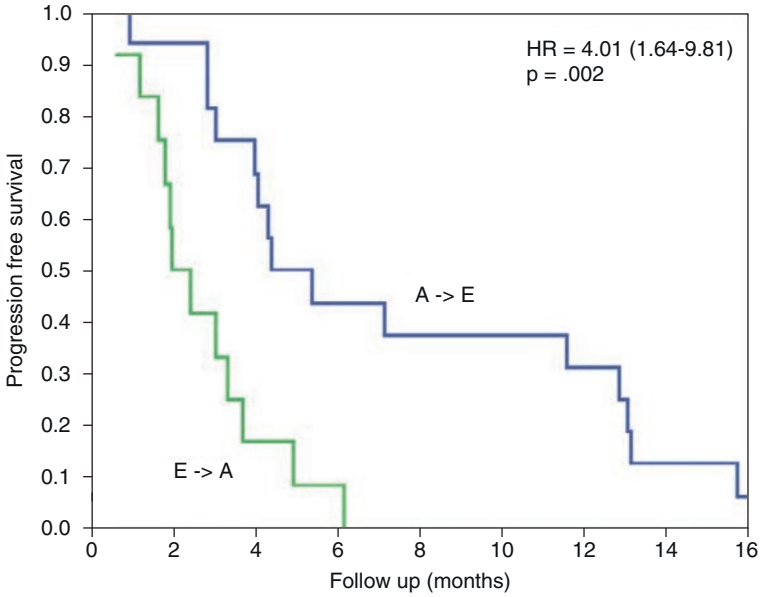
In a randomized clinical trial, clinical benefit in visceral sites was shown in patients exposed to exemestane versus anastrozole (38 vs. 32, respectively), as well as a longer survival 33.3 versus 30.5 months. Even though treatment with both AIs is generally well tolerated, it was demonstrated that exemestane is less likely to cause adverse events[5].

In trials analyzing adjuvant breast cancer treatment, exemestane, anastrozole, and letrozole have decreased the new incidence of contralateral breast cancer. Therefore, AIs, and maybe exemestane, are an alternative to manage contralateral breast cancer risk in postmenopausal women[6].



Treatment	II	Events	Censored	Median TTP (95% CI)
Exemestane	49	44	5	6.08 (2.52-9.65)
Anastrozole	51	44	7	12.07 (7.34-16.79)

Figure 3. Time to progression after the first-line therapy with aromatase inhibitor. The time to progression (TTP) after first-line aromatase inhibitor therapy is illustrated in postmenopausal patients with hormone receptor-positive, advanced breast cancer. Note that 3 patients, including 2 in the exemestane arm (E) and 1 in the anastrozole arm (A), were excluded from the analysis. HR: indicates hazard ratio; CI: confidence interval. *Source: Llombart-Cussac, et al.*[4]



	II	Events	Censored	Median TTP (95% CI)
Exemestane	16	15	1	4.41 (2.34-6,47)
Anastrozole	12	12	0	2.01 (1.17-2.84)

Figure 4. Time to progression (TTP) after the second-line therapy with aromatase inhibitor. TTP after second-line aromatase inhibitor therapy is illustrated in postmenopausal patients with hormone receptor-positive, advanced breast cancer. HR indicates hazard ratio; E: exemestane; A: anastrozole; CI, confidence interval. *Source: Llombart-Cussac, et al.*[4]

The results of a Phase II comparative trial showed anastrozole achieved better complete response than exemestane (46% vs. 36.2%), besides a longer DFI (12.1 vs. 6.1 months); however, despite these meaningful differences, the authors conclude that in a final review, exemestane is a better therapy than anastrozole[4].

CONCLUSION

So far, there is no conclusive evidence to choose a specific upfront AI for postmenopausal patients with hormone receptor-positive metastatic breast cancer. Although several trials appeared to demonstrate that letrozole and exemestane are a better option than anastrozole, in terms of response rate, clinically, more relevant studies in OS and DFS did not show significant differences among AIs[1].

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