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**ORIGINAL ARTICLE**

# Advanced breast cancer treatment, hormone-receptor-positive with endocrine therapy *versus* chemotherapy: economic analysis in the Brazilian Public Healthcare System (BPHS)

## Advanced breast cancer treatment, economic analysis

## *Tratamento do câncer de mama avançado, receptor hormonal positivo com terapia endócrina* versus *quimioterapia: avaliação econômica no Sistema Único de Saúde Brasileiro*

*Tratamento do câncer de mama avançado, avaliação econômica*

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## ABSTRACT

**Objectives:** To estimate the resource utilization and costs related to endocrine therapy (ET) versus chemotherapy (CT) in the treatment of hormone-receptor-positive (HR+) advanced breast cancer (ABC) patients after at least one previous ET. **Methods:** This retrospective longitudinal study analyzed ABC patients treatment with fulvestrant or CT from 2006 to 2008 in a public oncology outpatient service. Only patients without visceral crisis and with no less than one previous hormonal therapy were considered eligible. Medical charts were reviewed by two investigators and information about diagnosis, course of treatment, and resource utilization was obtained. **Results:** Patients were all female and the mean age was 64,6 ± 12,6 years. Patients were well-matched between groups considering baseline characteristics. Twenty-five patients were enrolled in the study, 13 patients received CT and 12 patients received fulvestrant. The most common CT regimen was paclitaxel (n = 5, 38%). The mean number of cycles was 7,6 and 5,8 for fulvestrant and CT, respectively. The mean treatment cost per patient was BRL 16,679 (USD11,914; 2005 purchasing power parity index 1USD = 1.4BRL) for fulvestrant and BRL32,946 (USD23,533) for CT. The avarage cost per cycle was BRL 2,199 (USD1,571) and BRL5,710 (USD4,079) for fulvestrant and CT, respectively, resulting in BRL3,511 (USD2,508) incremental cost per cycle. **Conclusions:** Our study results indicate that subsequent ET with fulvestrant can be economically appropriate among HR+ ABC patients. Further researches could validate these findings in other contexts, however we consider that our estimations reflect the real-world clinical practice in Brazil.

## Introduction

Hormone-receptor-positive (HR+) breast tumors represent 77% of all breast cancers (Jatoi *et al*., 2007). In postmenopausal HR+ breast cancer there are several endocrine therapeutic options available, of which selective estrogen receptor modulators (SERMs) and aromatase inhibitors (steroidal and nonsteroidal) have been largely studied and comprise the standard of care in breast cancer. Fulvestrant is a novel estrogen-receptor (ER) antagonist which differs from tamoxifen due to its lack of agonist activity (Chia *et al*., 2008). Expanding the hormonal therapeutic options to HR+ advanced breast cancer (ABC) is a well established necessity since the major part of patients diagnosed with ABC will present disease progression during the course of their treatment and additional endocrine agents will be required.

In Brazil, the public healthcare system covers only first and second-line treatment for ABC patients. Patients who progress after a second-line treatment do not have further endocrine therapeutic options and depend on local initiative

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**Table 1.** Hormone receptor positivity, previous endocrine therapy and visceral crisis data from chemotherapy clinical trials

| Study | Interventions | HR+ | Previous Endocrine Therapy | Visceral Crisis |
|---|---|---|---|---|
| O'Shaughnessy, 20028 | Capecitabine + Docetaxel | 39% | 32% (ADJ)<br>47% (ADV) | Not mentioned in the eligibility criteria. |
| | Capecitabine | 42% | 32% (ADJ)<br>54% (ADV) | |
| Chan, 19995 | Docetaxel | NI | 25% (ADJ)<br>33% (ADV)<br>12% (ADJ/ADV) | Exclusion criteria: pulmonary lymphangitic metastases, pleural effusion, and/or ascites as the only manifestation of disease. |
| | Doxorubicin | | 19% (ADJ)<br>32% (ADV)<br>20% (ADJ/ADV) | |
| Nabholtz, 20037 | Docetaxel + Doxorubicin | NI | NI | Exclusion criteria: lymphangitic carcinomatosis, ascites or pleural effusion as only manifestation of metastatic disease. |
| | Doxorubicin + Cyclophosphamide | | | |
| Jones, 20056 | Docetaxel | 56% | 47,6% (ADJ)<br>46,2% (ADV)<br>4,0% (ADJ/ADV) | Not mentioned in the eligibility criteria. |
| | Paclitaxel | 50% | 48,7% (ADJ)<br>45,1% (ADV)<br>4,5% (ADJ/ADV) | |

*Abbreviations:* NI, not informed; ADJ, adjuvant setting; ADV, advanced setting; ADJ/ADV, both adjuvant and advanced setting.

to access a third-line hormonal treatment. Those patients are eventually treated with chemotherapy protocols even when they are appropriate candidates to sequential hormonal therapy (patients without extensive visceral involvement which requires more rapid responses).

Existing evidence recommends the utilization of all available endocrine agents whenever clinically indicated (Barrios *et al*., 2009; Wilcken *et al*., 2003). Until this moment, comparative efficacy data between hormonal therapy and chemotherapy in ABC HR+ patients who progress after prior endocrine agents is not available. This lack of data can be explained by the fact that patients with more indolent and hormone sensitive disease would be preferentially treated with endocrine agents rather than chemotherapy. Selected clinical trials which have assessed the efficacy of protocols frequently used to treat this population in Brazilian clinical practice (capecitabine, docetaxel, paclitaxel, doxorubicin plus cyclophosphamide) showed baseline characteristics and eligibility criteria that differ from fulvestrant trials (Table 1) (Chan *et al*., 1999; Jones *et al*., 2005; Nabholtz *et al*., 2003; O'Shaughnessy, 2005).

Accordingly, Barrios *et al.* conducted a literature review about the role of chemotherapy in estrogen-receptor-positive (ER+) ABC. The authors discussed that recent chemotherapy clinical trials in ABC have enrolled patients despite their HR status, and chemotherapy treatment efficacy in patients with HR+ has not been reported separately compared with those with HR negative ABC (Barrios *et al*., 2009).

Three randomized phase III clinical trials have assessed the efficacy and safety of fulvestrant in women with ABC progressing after previous hormonal therapy compared to exemestane and anastrozole (Chia *et al.,* 2008; Howell *et al*., 2002; Howell *et al*., 2005; Robertson *et al*., 2003; Osborne *et al*., 2002). Results from these trials are presented in Table 2. More recently, a systematic review with meta-analysis has concluded that fulvestrant is similar to other endocrine agents with respect to efficacy with good tolerability profile (Valachis *et al*., 2009). Expanding hormonal therapeutic options with the incorporation of fulvestrant as further sequential endocrine agent could additionally extend the interval without chemotherapy for patients who would benefit from a better safety profile and the consequent improvement in quality of life.

In this context, the purpose of our study was to review the resource utilization and costs associated to the treatment of hormone sensitive ABC patients that attended a single Brazilian oncology practice during two consecutive years (2006-2008). Patients were analyzed by type of treatment: hormonal therapy with fulvestrant versus various chemotherapy protocols considered together. Each of the included patients and their direct medical costs were examined to analyze comparatively the economic impact of choosing between fulvestrant or chemotherapy after one-to-two pre-

**Table 2.** Major clinical trials evaluating fulvestrant in postmenopausal women with advanced breast cancer progressing after prior endocrine therapy

| Trial | Inclusion criteria | Exclusion Criteria | Line | Arms | No. of patients | Hormone receptor + (%) | Prior endocrine therapy: adjuvant [1st line; 2nd line] /metastatic (%) | Outcome | Results | Comparison |
|---|---|---|---|---|---|---|---|---|---|---|
| Chia et al., 2 EFECT trial | HR+ (ER and/or PgR), WHO performance status 0 to 2, life expectancy of at least 3 months, presence of at least one measurable or assessable lesion. It was allowed up to one prior chemotherapy regimen. | Life threatening metastatic visceral disease, brain or leptomeningeal metastasis, prior exposure to either fulvestrant or exemestane, extensive radiation or cytotoxic therapy within the last 4 months, or history of bleeding diathesis or need for long-term anticoagulation. | Second or Third | Fulvestrant | 351 | 98.3 | 61.8 [41.3; 58.7] | Median TTP (months) | 3.7<br>3.7 | HR: 0.96 (95% CI 0.82–1.13)<br>P-value = 0.65 |
| | | | | | | | | ORR (% pts) | 7.4<br>6.7 | OR: 1.12 (95%CI 0.58–2.19)<br>P-value = 0.74 |
| | | | | Exemestane | 342 | 98.2 | 58.2 [43.0;57.0] | CBR (% pts) | 32.2<br>31.5 | OR: 1.03 (95%CI 0.72–1.49)<br>P-value = 0.85 |
| | | | | | | | | DOR (months) | 13.5<br>9.8 | NA |
| Phase III Trials 002010 and 002112 combined analysis 9, 11 | Tumor evidence of hormone sensitivity (prior sensitivity to hormonal therapy or known ER or PgR positivity), WHO performance status 0 to 2, life expectancy of at least 3 months, presence of at least one measurable or assessable lesion. | Life threatening metastatic visceral disease, brain or leptomeningeal metastasis, prior exposure to either fulvestrant or any aromatase inhibitor, more than one prior endocrine medical treatment for ABC, extensive radiation or cytotoxic therapy within the last 4 months, estrogen replacement therapy within 4 weeks to randomization, treatment with luteinizing hormone-releasing hormone analogs within 3 months before randomization, and any concurrent illness that would compromise safety or prevent interpretation of results. | Second | Fulvestrant Anastrazole | 428 | 79.9 | 56.8/55.1 | Median TTP (months) | 5.5<br>4.1 | HR: 0.95 (95% CI 0.82–1.10)<br>P-value = 0.48 |
| | | | | | | | | ORR (% pts) | 19.2<br>16.5 | Difference in ORR: 2.75 (95% CI 2.27–9.05)<br>P-value = 0.31 |
| | | | | | 423 | 83.2 | 55.6/ 53.4 | DOR (months) | 16.7<br>13.7 | HR: 1,30 (95% CI 1.13–1.50)<br>P-value < 0.01 |
| | | | | | | | | OS (months) | 27.4<br>27.7 | HR: 0,98 (95% CI 0.84–1.15)<br>P-value = 0.89 |

Abbreviations: ABC, advanced breast cancer; No., number; OS, overall survival; HR+, hormone-receptor-positive; ER, estrogen-receptor; PgR, progesterone-receptor; HR, hazard ratio; CI, confidence interval; TTP, time to progression; ORR, objective response rate; OR, odds ratio; CBR, clinical benefit rate; DOR, duration of response (from randomization to disease progression); NA, not available.

vious hormonal lines of treatment in patients without visceral crisis (the main criteria to define sequential hormonal therapy or chemotherapy among those patients). This retrospective study attempts to identify economic outcomes in this population once the clinical benefit of the sequential endocrine treatment is well established in the medical literature. This information is not currently available and could help doctors, patients and decision leaders to select the most clinical and economic beneficial therapeutic option in hormone-receptor-positive ABC progressing after previous hormonal therapy.

## Methods

### *Study sample*

This retrospective longitudinal study analyzed ABC patients receiving hormonal therapy between August 2006 and August 2008 in the oncology outpatient service at Pérola Byington Public Hospital (PBPH), São Paulo, Brazil. Patients were included in the fulvestrant study group if they met the following requirements: A) female; B) documented diagnosis of ABC with evidence of hormone sensitivity (i.e., prior sensitivity to hormonal therapy or known ER or progesterone receptor positivity); C) postmenopausal status; D) previous exposure to one or two hormonal therapies; E) subsequent fulvestrant treatment with at least two completed cycles. Exclusion criteria included the following: presence of visceral crisis, defined as pulmonary lymphangitic spread, pericardial effusion, any extensive visceral involvement or/and symptomatic visceral metastasis. The study sample was a convenience sample and included all eligible patients identified in the PBPH patient database.

To identify patients for the chemotherapy group, the same eligibility criteria were applied to patients who had received chemotherapy protocols at the PBPH. As fulvestrant is not broadly available in the Brazilian Public Health System (BPHS), some hormone-receptor-positive patients are currently treated with various chemotherapy protocols. All chemotherapy patients were strictly reviewed according to eligibility criteria and, in the opinion of the investigators, all were deemed appropriate candidates for subsequent hormonal therapy at the time the chemotherapeutic treatment was started. Only patients who received at least two cycles of the prescribed chemotherapeutic protocol were included.

### *Data Collection and Analysis*

Medical charts were reviewed by two independent investigators for the duration of the prescribed treatment after the failure to first or second-line hormonal therapy and for the information about their diagnosis, course of treatment, and resource utilization obtained. The following information was extracted from their charts: age, stage, first breast cancer diagnosis date, histological type of tumor, ER/PgR status, HER2 status, metastasis diagnosis date, sites of metastasis, disease extension, previous systemic treatments (dates and types), radiation therapy (dates and locations), breast cancer-related surgeries, and data from fulvestrant or chemotherapeutic treatment after one or two previous hormonal therapies (medications, dosage, duration, number of cycles, and concomitant resource utilization). Only direct medical costs were included in the resource utilization analysis: medications, outpatient visits, medical procedures, hospitalizations etc. As the purpose of this study is not to evaluate clinical benefit from each treatment, clinical outcomes data were not collected. This study was performed after approval by a local institutional review board in accordance with Brazilian regulatory dispositions.

Data on resource use for each patient in our study sample were extracted from the medical chart. For each resource collected, a specific unit cost was attributed. These data were used to estimate the direct medical resource use and cost to each group (fulvestrant versus chemotherapy). The treatment costs were calculated multiplying the resource utilization by the respective unit costs. The unit costs for 2008 were obtained from Brazilian Public Health Service official listings and, for medications, the generic drug price was considered. All resource use and costs were calculated per patient and per cycle of treatment. Mean values are reported ± SD (standard deviation). All costs are given in Brazilian Real (BRL) and US Dollars (USD) using 2005 Purchasing Power Parity Index (1 USD = 1,4 BRL) (World Bank, 2009 ).

## Results

The demographic and clinical characteristics of the sample of 25 patients at the study entry are listed in Table 3. Patients were all female and the age ranged from 41 to 88 years (mean 64,6 ± 12,6 years). The year of the first breast cancer diagnosis ranged from 1992 to 2004. Patients were well matched between groups considering baseline characteristics. Thirteen patients had received chemotherapy and 12 patients had received fulvestrant. The most common chemotherapeutic regimen was paclitaxel alone (n = 5, 38%), followed by other four different protocols.

Direct medical cost resource use within the study population is shown in Table 4. Resources are presented in the table when they are more frequent than 0,5 unities per patient during the entire treatment. The mean number of cycles was 7,6 and 5,8 for fulvestrant and chemotherapy patients, respectively. The distribution of chemotherapy protocols prescribed after first or second-line hormonal therapy was: paclitaxel alone (n = 5, 38%), gemcitabine plus cisplatin (n = 3, 23%), paclitaxel plus carboplatin (n = 3, 23%), capecitabine (n = 1, 8%) and fluorouracil plus epirubicin and cyclophosphamide (n = 1, 8%).

The estimated costs per treatment, per patient and per cycle to each group are shown in Table 5. The average cost

**Table 3.** Baseline data

| | Fulvestrant n = 12 | Chemotherapy n = 13 |
|---|---|---|
| Age (years) | 66.9 ± 12.7 | 62.6 ± 12.6 |
| Histological type – Infiltrating Ductal Carcinoma (%) | 83.3% | 84.6% |
| Histological type – Other (%) | 16.7%a | 15.4%b |
| Postmenopausal status at diagnosis (%) | 76.9% | 83.0% |
| Previous neoadjuvant treatment (%) | 25.0% | 30.7% |
| Duration of disease at the study inclusion (years) | 6.9 ± 3.6 | 6.6 ± 3.9 |
| Time from first breast cancer diagnosis to first metastasis diagnosis (years) | 4.0 ± 3.3 | 4.6 ± 2.4 |

a One patient with infiltrating lobular carcinoma and one patient with bilateral infiltrating ductal carcinoma

b One patient with invasive papillary carcinoma and one patient with bilateral infiltrating ductal carcinoma

**Table 4.** Comparison of resource utilization through the treatment duration

| | Fulvestrant n=12 | Chemotherapy n = 13 |
|---|---|---|
| Treatment cycles | 7.6 | 5.8 |
| Outpatient visits – Oncologist | 6.17 ± 3.72 | 4.69 ± 1.77 |
| Outpatient visits – Other Specialist | 0.25 ± 0.60 | 0.46 ± 1.08 |
| Biochemical laboratory tests (Sodium, Potassium, Glucose) | 0.83 ± 0.99 | 1.23 ± 1.80 |
| Complete Blood Count | 0.92 ± 0.95 | 1.62 ± 1.39 |
| Urea | 0.75 ± 0,83 | 1.0 ± 1.84 |
| Creatinine | 0.75 ± 0.83 | 1.0 ± 1.84 |
| CA 153 | 1.58 ± 1.38 | 0.69 ± 0.91 |
| Chest Radiography | 0.58 ± 0.86 | 0.46 ± 0.63 |
| Chest Tomography | 0.17 ± 0.37 | 0.69 ± 0.72 |
| Abdominal Ultrasound | 0.58 ± 0.76 | 0.46 ± 0.50 |
| % Bisphosphonates | 16.6% | 41.6% |
| Bisphosphonates infusions | 3.0 ± 0.0 | 6.4 ± 2.8 |
| % Hospitalization (non ICU) | 16.7% ± 37.3% | 30.8% ± 46.2% |
| Hospitalization days (non ICU) | 6.5 ± 3.5 | 13,25 ± 5.36 |

of treatment within the chemotherapy population was higher compared with patients treated with fulvestrant. The mean treatment cost per patient was BRL 16,679 (USD 11,914) for fulvestrant patients and BRL 32,946 (USD 23,533) for chemotherapy patients. The mean cost per cycle was BRL 2,199 (USD 1,571) and BRL 5,710 (USD 4,079) for fulvestrant and chemotherapy, respectively, resulting in BRL 3,511 (USD 2,508) incremental cost per cycle. Medications were the largest contributor to overall cost in both groups, corresponding to 97% and 92% of total costs per cycle in the fulvestrant and chemotherapy groups, respectively.

## Discussion

This study used retrospective medical chart review to estimate direct medical resources spent and treatment costs. Direct medical costs and resource use were higher for chemotherapy treatment when compared to fulvestrant treatment. Medications were the largest contributors to overall cost.

To our knowledge, there are no recent studies that have investigated treatment costs related to hormonal therapy versus chemotherapy in patients with hormone-receptor-positive breast cancer in Brazil. Cost-effectiveness analysis in this setting is not feasible, once comparative efficacy data from head-to-head studies or indirect comparisons are not available. This absence of data seems logical since the current evidence available dictates sequential hormonal therapy for patients without visceral crisis due to the demonstrated efficacy and favorable toxicity profile of endocrine therapy among this population – as indicated by our literature review.

**Table 5.** Comparison of estimated costs

| | Fulvestrant | | Chemotherapy | | Incremental | |
|---|---|---|---|---|---|---|
| | BRL | USD | BRL | USD | BRL | USD |
| Total treatment cost | 200.150 | 142.965 | 428.298 | 305.928 | 228.148 | 162.963 |
| Treatment cost per patient | 16.679 | 11.914 | 32.946 | 23.,533 | 16.266 | 11.619 |
| Treatment cost per cycle | 2.199 | 1.571 | 5.710 | 4.079 | 3.511 | 2.508 |

*Abbreviations*: BRL, Brazilian Reais; USD, United States Dollars.

Two European studies have recently analyzed the cost-utility of fulvestrant-containing sequences of treatment for ABC (Cameron *et al*., 2008; Lux *et al*., 2009). Both studies compared costs and clinical benefit (in terms of QALY - *Quality Adjusted Life Year*) of treatment sequences with and without fulvestrant, i.e., the economic analysis aimed to investigate whether an additional treatment step with fulvestrant in a sequence of hormonal treatments for ABC and the resulting postponement of subsequent chemotherapy are cost-effective options in this scenario. The British study compared sequences containing/omitting fulvestrant as second and third-line option and the German study focused on fulvestrant as second-line only. They found a favorable scenario to fulvestrant-containing sequences in third-line and second-line options in the UK and Germany studies, respectively.

In terms of limitations to our study, retrospective studies are prone to a certain degree of bias. Medical chart reviews depend on how detailed physician's records are in daily clinical practice and some resources actually used could be missed in studies like ours. This situation would tend to underestimate the direct medical cost in both groups. If we judge that chemotherapy treated patients are more liable to consume a larger amount of resources due to toxicity management, for example, we could consider that this bias source has potential to underestimate the incremental cost. Another limitation was the small sample size. Fulvestrant is not officially covered by Brazilian Public Health System and its availability depends on local initiatives, thus being restricted to the number of patients who had received fulvestrant in our reality.

The particularities of each healthcare system can affect the generalizability of data from local resource utilization and cost studies. Socioeconomic factors and factors related to local treatment patterns that influence the direct medical resource utilization and costs can be different in other scenarios.

## Conclusions

Our study results and literature review can indicate that subsequent hormonal therapy with fulvestrant is clinically and economically appropriate in this setting. Further researches could validate these findings in other contexts and populations, but we consider that our estimation reflects the real-world clinical practice in Brazil.

In conclusion, this study has shown that, if fulvestrant is available to clinically eligible patients in the Brazilian setting, its economic impact is more favorable than chemotherapy's. This type of study is likely to be important to policy-makers and physicians concerned with rational resource allocation.

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