Transversal Study of Breast Cancer Treatment in Spain

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Abstract

Objectives: The study's objectives were to observe and describe chemotherapy treatment (CT) used in breast cancer (BC) patients in Spain and estimate its cost.

Methods: Multi-centre and transversal study, which included consecutive BC patients treated with chemotherapy between 10 and 15 May 2004 in 110 centres throughout Spain. Information was gathered on the general characteristics of the centres, the patient data and the treatments administered. This information was collected prospectively based on the data available in the pharmacy service and/or the patient's clinical history. The following information was requested: demographic, clinical, CT administered during the week of the study, established guidelines, inclusion in clinical trials, and the direct costs of the medication.

Results: A total of 2134 patients were included (99.7% women) from 16 autonomous communities and the average age was 51.5. The majority of the treatments were administered in general hospitals (89.7%), public or public health partnership hospitals (91.5%), and level 3 specialist hospitals (64.5%). Among these patients, 120 (5.6%) received treatment as part of a clinical study. A total of 51% of patients received adjuvant or neoadjuvant treatment, mainly for stage IIA disease (28.7%). A total of 1011 patients presented metastatic disease (MD). The estimated average cost of chemotherapy treatment was €428.5 per cycle and the group of patients with MD incurred the greatest cost (€640.4 per cycle).

Conclusions: The results show the current situation of CT for BC in Spain and a great deal of variability is observed both in the use of drugs as well as in the associated costs.

Key words: Breast cancer. Chemotherapy. Adjuvant. Neoadjuvant. Metastatic disease. Cost.

Part of the results of this study was presented at the congress of the American Society of Clinical Oncology (ASCO 2005) and the 50th Conference of the Spanish Society of Hospital Pharmacy (2005).

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Estudio transversal del tratamiento del cáncer de mama en España

Objetivos: Los objetivos del estudio fueron conocer y describir el tratamiento quimioterápico (QT) en pacientes con cáncer de mama (CM) en España y estimar su coste.

Métodos: Estudio multicéntrico y transversal en el que se incluyó a todos los pacientes consecutivos con CM tratados con quimioterapia entre el 10 y el 15 de mayo de 2004 en 110 centros de España. Se recogió información de las características generales de los centros y datos de los pacientes y tratamientos administrados, la cual se realizó de manera prospectiva a partir de los datos disponibles en el servicio de farmacia y/o en la propia historia clínica. Se solicitaron datos demográficos, clínicos, tratamientos QT administrados durante la semana de estudio y protocolos previos, así como la inclusión en ensayos clínicos y los costes directos de la medicación.

Resultados: Se incluyó a 2.134 pacientes (el 99,7% mujer; edad media, 51,5 años) de 16 comunidades autónomas. La mayoría de los tratamientos se administró en hospitales generales (89,7%), públicos o concertados (91,5%) y de nivel 3 (64,5%). De ellos, 120 pacientes (5,6%) recibieron tratamiento en un ensayo clínico. El 51% de los pacientes recibió tratamiento adyuvante o neoadyuvante, principalmente por enfermedad en estadio IIA (28,7%). En total, 1.011 pacientes presentaron enfermedad metastásica (EM). El coste medio estimado del tratamiento quimioterápico fue de 428,5 \in /ciclo, y las pacientes con EM constituyeron el grupo con un mayor coste (640,4 \in /ciclo).

Conclusiones: Los resultados presentan una visión de la situación real del tratamiento QT del CM en España, y se observa una amplia variabilidad, tanto en la utilización de fármacos como en los costes asociados.

Palabras clave: Cáncer de mama. Quimioterapia. Adyuvancia. Neoadyuvancia. Enfermedad metastásica. Coste.

INTRODUCTION

Breast cancer (BC) is one of the largest public health problems in the developed countries, not only in terms of frequency but also mortality, because it is the most common malignant tumour and is the main cause of death from cancer among the female population. The current likelihood of a Spanish woman presenting BC before the age of 75 is 8%,¹ and it is estimated that 1 out of 9 Spanish women will develop this disease at some time of their lives. According to the report La situación del cáncer en España (The situation of cancer in Spain),² each year, 16 000 new cases of BC are diagnosed and around 6000 deaths are registered.^{3,4} The age-adjusted rate in 1998 was 67/100 000 women, the lowest in the European Union,^{2,3} but the number of new diagnoses between 2000 and 2005 (67 000) situates Spain in line with the rest of the countries in Europe. Different factors, among them the progressive ageing of the population, have contributed to the increased rate in recent years. At the same time, society's greater awareness of the importance of early diagnosis and the existence of screening programmes have led to an increasing number of patients being diagnosed with the disease in the early stages and being able to benefit from a greater likelihood of cure. All this, together with the appearance of more and better treatments as a result of the most recent advances in the understanding of the biology of cancer and the increase in survival (>75% after 5 years from diagnosis),³ constitute one of the main causes of the increased rate in BC observed in recent years.

The treatment of breast cancer is complex and varied. Conceptually, it includes, with the exception of the in situ treatment carcinoma lobular of the local disease by surgery and/or radiotherapy, the systemic treatment of the disease with chemotherapy (CT) and/or hormones. The need for and choice of the different local or systemic treatments is based on different prognostic and predictive factors, which include histology, the clinical characteristics of the primary tumour, lymph node involvement, the hormone receptors, *HER2/neu* expression levels, the presence or absence of detectable metastatic disease, concurrent disorders, patient age, and ovarian function.⁵

Medical practice variations (MPV) are defined as systematic (rather than random) variations in the standard rates of use of certain treatments, or important aspects of these, with respect to a value sensitive to aggregation to the population.⁶ The study of MPV in Spain is relatively recent, but it has confirmed that a good part of what has been described in other countries (mainly in the United States, the United Kingdom, and the Nordic countries) is also happening in our environment. In the oncology area, the work done by the the Agency for Evaluating Healthcare Technology of Andalusia (AETSA, *Agencia de Evaluación de Tecnologías Sanitarias de Andalucía*),^{7,8} the National Institute of Clinical Excellence (NICE),⁹ and the Karolinska Intitute¹⁰ on the variations in use of cytostatic treatments is important. MPV are important because they are frequent and systematic, and they have an impact on the cost of the treatments and their

results. Understanding their causes is a complex matter, but neither the introduction of new technologies nor aspects depending on the population, or the different demographic composition, specific epidemiological circumstances of the populations compared or differences in accessibility for economic reasons, are such deciding factors as the services available and the attitude of the supplier of these services.¹¹ With regard to this point, 3 possible causes for the variations have been identified: a) uncertainty felt by doctors faced with the large range of treatments available and the lack of sufficiently rigorous research; b) unfamiliarity of the new research and its results; and c) doctor preference. There is some consensus when it comes to considering the first of these the most influential factor, but it is essential to consider the weak relationship existing between the true situation of medical science and the true situation of clinical practice as another cause of the variations.

Medical science is looking for a better clinical response in specific situations, while clinical practice seeks to respond to the patient for whom there may be no clearly defined treatment options. This may be the case in patients with metastatic disease after the failure of the first and second line treatment. In the case of MPV caused by uncertainty, the preparation and implantation of clinical practice guides (CPG) based on the best scientific evidence available would appear to be the best tool for guaranteeing that patient groups with specific clinical conditions receive the treatment recommended by the scientific community.^{14,15} Different studies have shown that when the treatment of cancer is protocolised, better clinical results are obtained in terms of lower mortality and morbidity. Nevertheless, earlier studies showed that the degree of fit of chemotherapy treatments to the CPG is not uniform and depends on several factors, including the type and level of specialisation of the centres,^{16,17} healthcare professionals' workload,18 and the characteristics of the disease,19 among others.

If we focus on the analysis of variations in the treatment of BC, the treatment of this disease has been described in several international studies.^{20,21} In Spain, there is data from the GEICAM²² group available, but to date there has been no study in Spain that has specifically tackled the variability of CT treatment in women with BC, nor has there been an analysis of the associated costs. The study's objectives were to observe and describe intravenous chemotherapy treatment (CT) used in breast cancer (BC) patients in Spain and according to the autonomous region, hospital type and size, analyse the impact of age on treatment choice, ascertaining the percentage of patients included in research phase protocols and estimate the cost of the CT treatments administered.

METHOD

A cross-sectional, multi-centre study was designed, which included all the consecutive patients with a diagnosis of BC who received intravenous CT treatment between 10 and 15 May 2004 in 110 participating centres. All the pharmacy services in the hospital centres with representatives of the GEDEFO group were invited to participate on a voluntary basis.

An ad hoc form was designed for the purpose of gathering the data from the centres. The forms were completed before the start of the study and sent to the GEDEFO headquarters for a centre code to be assigned that would ensure the mask during the analysis. Information was gathered regarding the general characteristics of the centres (type: general/oncological, funding: publicassigned/private), structure (level), area of influence, and clinical activity. Level 1 was defined as district or low complexity, level 2 as general or average complexity, and level 3 as reference, high technology or highly complex. A specific form was also designed for gathering the data about the patients and the treatments administered, which would be collected prospectively on the week of the study from the data available at the pharmacy service and/or the medical history itself. Demographic (age), clinical (stage of the disease), CT treatment administered during the week of the study, and previous protocols (cytostatics, doses, previous number of cycles) information, as well as data about the service responsible for the prescription were gathered. The form also included a section for indicating whether the patients were included in any protocols in the research phase when necessary. Only information regarding iv cytostatics was gathered (including trastuzumab) and all supporting medication was excluded. Oral treatment was only considered if administered combined with or consecutively to other intravenous cytostatics. The clinical trial treatments were analysed separately. Each patient was considered once only, regardless of treatments administered on consecutive or alternate days. Previous treatments were considered to be all CT regimens different from those applied in the study and administered prior to this.

The cost analysis was made based on the information completed in the data collection formula provided by the centres, that is to say, based on the information about the drug and the dose, the cost for the period was calculated (from 10 to 15 May). Only the direct purchase cost (in euros) of the cytostatics administered during the inclusion period was considered, and cost per cycle was estimated based on this information. A treatment cycle was defined as the sequence of drugs administered during a certain time according to the administration schedule. To determine this, the manufacturer's sale price (RRP)/mg (VAT excluded) was calculated for each cytostatic at January 1, 2004.23 In cases where there was more than one presentation available, the RRP/mg of the highest dose presentation of the cytostatic was used. The data is presented per autonomous region. The autonomous regions with small samples were added and treated jointly. The statistical analysis was carried out in 2 stages with the SPSS statistical package, version 9.0 (SPSS Inc.). In the first stage, descriptive methods were applied to calculate the distribution rate of the qualitative endpoints. In the case of the qualitative endpoints, we then calculated the central trend and dispersion measurements, as well as the typical deviation and endpoint range. In the second, the χ^2 test was applied. The significance level applied to the

different hypothesis tests was $P \le .05$, with a likelihood of 80%. All the tests were bilateral. (Although a small number of male patients were included in the study, from now on the feminine gender will be used to refer to the patients included.)

RESULTS

A total of 2134 patients (99.7% women) were included in 110 centres in 43 provinces and 16 autonomous regions. Catalonia (n=23), Andalusia (n=15), and the Autonomous Region of Madrid (n=14) were the autonomous regions with the largest number of participating centres. Catalonia with 425 patients, the Autonomous Region of Valencia with 279 patients, and Andalusia with 250 patients were the autonomous regions that included the largest number of patients. The average age of the patients was 51.5 years (interval, 23-87). Seventy-one point two percent of the sample was aged between 36 and 65 years of age (Table 1).

Description of the Participating Centres, Scope of Treatment, and Prescribing Services

Table 2 shows the clinical characteristics of the centres. The majority were general hospitals (94.5%), public or partly private hospitals (90.0%), and 2nd level hospitals (43.6%). In general terms, these were also the centres that included the largest number of patients. However, the number of patients treated in 3rd level hospitals (64.5%) was higher than that treated at 2nd level centres (25.8%). Almost all the treatments (99.2%) were administered in the day hospital. The oncological medical service was responsible for 93.2% of the prescriptions, followed by the gynaecology service (6.0%). No other services other than those mentioned are responsible for prescribing CT treatments.

Intention of the Treatment and Stage of the Disease

Forty-nine percent of the treatments administered during the period studied were administered to patients with metastatic

Table 1. Distribution of Patients According to Ag	e Groups
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Age, y	Percentage	Intention of Treatment		
		Adjuvant,	Neoadjuvant,	Metastatic
		%	%	Disease,
				%
≤35	4.1	3.6	9.4	3.8
36-50	34.6	35.7	48.6	31.0
51-65	36.6	37.3	20.3	38.3
66-75	16.4	16.3	14.5	18.1
>75	4.5	3.7	2.6	5.9
Unknown	3.8	4	4.3	3

Table 2. Characteristics of the Participating Centres

Characteristics	No. (%)	Patients (%)	
of the Centres			
Type of centre			
General	104 (94.5)	1914 (89.7)	
Oncological	6 (5.5)	203 (9.5)	
Funding			
Public/partly private	99 (90.0)	1952 (91.5)	
Private	10 (9.1)	140 (6.6)	
Level			
1	17 (15.5)	137 (6.4)	
2	48 (43.6)	551 (25.8)	
3	42 (38.2)	1376 (64.5)	

disease, 46.2% in adjuvance, and 7.9% in neoadjuvance. When the previous CT treatments were taken into consideration, it was observed that in the majority of cases, the first CT treatment was administered in adjuvance (60.7%), ahead of the treatments for metastatic disease (20.8%), and the neoadjuvant treatments (18.5%). With regard to the neoadjuvant treatments administered during the week of the study, the percentage of these administered at level 1 centres (9.5%) represented an important proportion of the total which, as has been observed, is higher than that at 2nd level centres (2.5%) and 3rd level centres (7.6%).

Table 3 shows the distribution of patients according to the stage of the disease and the intention of the treatment. Around 50% of the patients receiving adjuvant treatment presented stage II disease. Around 55% of the patients with neoadjuvant treatment presented stage III disease.

Clinical Trials

A total of 120 patients (mainly in the Autonomous Region of Valencia [26.7%], Catalonia [19.2%], Andalusia [18.3%], and

Table 3. Distribution of Patients by the Stage of the Disease			
Stage	Adjuvant	Neoadjuvant	Metastatic
	Treatment, %	Treatment, %	Disease
	18.9	1.4	-
IIA	31.1	15.9	-
IIB	18.4	15.9	-
IIIA	15.8	27.5	-
IIIB	3.8	25.4	-
IIIC	4.3	2.2	-
IV	0	0	49
Unknown	7.7	11.6	-

Madrid [13.4%]) distributed among a total of 37 centres received CT treatment in protocols in the research stage, a figure representing 5.6% of the sample. The average age was 50.0 years (interval, 25-80). The majority of patients were treated in general (79.2%), public/partly private (95%), and 3rd level (85.5%) hospitals, in comparison to monographic (20.8%), private (4.2%), and 1st and 2nd levels (3.3% and 10%, respectively) hospitals. Nevertheless, in relation to the number of patients treated by type of hospital, the monographic centres included more patients in CT (12.3%) than the general hospitals (5%). Of the total CT, 50 (41.7%) corresponded to adjuvant treatments, 36 (30%) to neoadjuvant treatments, and 34 (28.3%) to metastatic/palliative treatments (21 in first line, 9 in second line, 2 in third line, and 2 in fifth line or more). With regard to the total patients in each treatment group, the treatments in CT corresponded to 5.5%, 20.7%, and 3.3% of the adjuvant, neoadjuvant treatments and treatments for metastatic disease, respectively. Statistically significant differences were observed in the percentage of patients included in CT according to age groups (≤ 65 years and > 65 years) (Figure 1).

Chemotherapy Treatments

A total of 859 patients received off-protocol adjuvant treatment in the research stage. Of these, 51.4% received at least an anthracycline in AC-type regimens (doxorubicin, cyclophosphamide), FAC (5-fluorouracil, doxorubicin, cyclophosphamide), EC (epirubicin, cyclophosphamide) or FEC (5-fluorouracil, epirubicin, cyclophosphamide), the latter of these being the most frequent (n=257). Twenty-one point five percent of the patients received a taxane (49.4% combined with anthracycline, 44.9% in monotherapy and 5.7% in combination with other cytostatics) and 21.2%, treatment with BCF (cyclophosphamide, methotrexate, 5-fluorouracil). The analysis by age groups revealed that the use of CMF increased with age, representing 59% of the treatments in patients >75 years. The use of anthracyclines was relatively constant in the group of patients



Figure 1. Patients included in clinical trials by age group.



Figure 2. Use of CMF (cyclophosphamide, methotrexate, 5-fluorouacil) and anthracyclines in adjuvance according to age group.

aged ≤ 65 years, although an important decrease was seen from this age on (Figure 2). Paclitaxel was the most frequently administered taxane (53.0%), which epirubicin was the anthracycline of choice in 59.0% of cases.

In the group of patients receiving neoadjuvant treatment outside a clinical trial (138), 42% received treatment based on AC, FAC, EC and FEC anthracyclines, 26.8% combined treatment with taxanes and anthracyclines, and 18.1% taxanes alone. A greater use of docetaxel (72.7%) and epirubicin (53.4%) was observed (Figure 3).

The number of patients on treatment for metastatic disease included in CT was 1011. Of these 41.9% received first line treatment, 27.8% second line, 14.5% third line, 9.8% fourth line, and 4.9% fifth line or subsequent. A total of 30.7% of the patients on first line treatment received trastuzumab (43.1% combined with paclitaxel, 24.6% in monotherapy, 23.1% combined with vinorelbine, and 9.2% combined with docetaxel), 22.0% taxanes in monotherapy, 17.0% taxanes in combined treatment (58.3% with anthracylines, 18.0% with capecitabine, 13.8% with gemcitabine, 5.5% with vinorelbine, and 4.2% with carboplatin), and 7.8%, anthracylines in AC, FAC, EC and FECtype protocols. A total of 4.0% of the patients receiving first



Figure 3. Use of taxanes and anthracyclines in patients with neoadjuvant treatment.

line treatment with anthracyclines had received anthracyclines in previous treatments.

Cost Analysis

The overall cost of the treatment of the 1886 assessable patients was €808.071. The average national (standard deviation [SD]) was 428.4 (566.5) €/cycle; the Autonomous Region of Valencia (581.8 [806.8] €/cycle) and the Basque Region (281 [368.6] €/cycle) were the autonomous regions showing differences in comparison to the Spanish national average (Table 4).

According to the intention of the treatment, the group of patients with metastatic disease was the highest cost group associated with cytostatics per patient and cycle (≤ 640.4 /cycle), followed by patients on neoadjuvant treatment (≤ 232.5 /cycle) and the patients with adjuvant treatment (≤ 180.1 /cycle). However, it was this final group in which the greatest variability in costs was seen. By age, a larger expense in patients ≤ 65 years was seen, with the exception of the treatment administered in the neoadjuvant context. The cost per patient and per cycle is similar, regardless of the characteristics of the structure of the centres (Figure 4).

	No.	Total, €	Average (SD)	95% Cl	Median
Spain	1886	808 071	428.4 (566.5)	403-454	182.7
Andalusia	216	98 023	453.8 (580.6)	375-532	201.3
Castilla-La Mancha	80	35 717	446.5 (486.7)	338-555	223.4
Castilla y León	103	35 816	347.7 (514.7)	247-448	175.6
Catalonia	320	127 169	397.4 (511.5)	341-453	182.3
Valencia	227	132 357	588.1 (806.8)	477-689	297.4
Galicia	195	87 978	451.2 (606.5)	365-536	154.0
Madrid	175	69 312	396.1 (501.1)	321-470	154.7
Basque Country	146	41 056	281.2 (368.6)	221-341	160.8
Other regions	329	180 639	414.2 (509.3)	358-469	191.55

Table 4. Cost of Chemotherapy Treatment (€/Cycle) per Autonomous Region^a

aCI indicates confidence interval; SD, standard deviation.



Figure 4. National average cost of adjuvant chemotherapy, neoadjuvant, and treatment for metastatic disease (MD).

DISCUSSION

This is the first study to have been conducted in Spain for the purpose of understanding and describing intravenous chemotherapy treatment in patients with BC. It is estimated that the set of areas of influence of the participating centres covered around 70.0% of the Spanish population (43 048 851, year 2004).²⁴ Likewise, considering the population of women in the year 2004 and an annual rate of breast cancer of 45-75 new cases for every 100 000 women,² and assuming that 70% of the patients with non-metastatic disease receive CT treatment and that the average number of chemotherapy cycles in adjuvancy and neoadjuvancy is 6, it is estimated that during the week of the study, around 76% of the patients receiving chemotherapy during this period were selected. The descriptive nature of the study requires a cautious interpretation of the results, nevertheless, if we address the large sample of patients included in different levels of centre throughout Spain, the data presented here can be considered to be highly representative of chemotherapy treatment for breast cancer in Spain.

Since the publication of the initial studies on the activity of BCF in women with metastatic disease during the 1970s, a large number of therapeutic options have contributed to the improved control of this group of patients. In the chemotherapy area, the appearance of anthracylines during the 1980s and taxanes in the 1990s has been important. More recently, biomedical advances have favoured the development of new molecules which, nowadays form part of an extensive therapeutic arsenal available to patients with metastatic disease, which includes, in addition to the above mentioned cytostatics, vinorelbine, cysplatin, carboplatin, gemcitabine, liposomal doxorubicin, and trastuzumab. The data obtained confirms that there are great variations in the use of these drugs and in the way they are combined in our country, a fact which becomes more evident as the number of lines of treatment increases due to the reduced scientific evidence available in these cases. The fact that the new, generally more expensive drugs are introduced for the treatment of metastatic disease contributes to the cost of treating these payments being higher than that for patients on adjuvant or neoadjuvant treatment. Different studies have analysed the efficacy of these treatments.^{25,26}

Correspondingly, during the 1970s the first clinical studies were also conducted in patients with early stage disease and showed that the administration of chemotherapy with adjuvant intention increased survival. Later studies have shown that polychemotherapy offers advantages over monotherapy in terms of benefit, that the optimum duration of the treatment should be 6 months and that anthracyclines are slightly more active than the classic treatment with BCF. However, the role of taxanes in adjuvancy must still be defined, although recent studies indicate its role in the sequential or combined treatment with anthracyclines in women with lymph node involvement.²⁷⁻³³ The study data indicate that by 2004 taxanes were being used outside the context of a clinical trial in 22% of patients in our country. During recent years there has also been a tendency to administer the chemotherapy prior to the surgical intervention. Randomised studies in patients with stage II, IIIA, and IIIB disease have shown, for example, that neoadjuvant chemotherapy enables the percentage of patients with conservative surgery to be increased. In this group of patients, the classic treatment is based on anthracyclines and/or taxanes.34 However, it is certain that the use of this method of treatment requires extensive coordination within the healthcare team, which is why it is surprising that the percentage of patients treated in neoadjuvancy is greater with regard to the total patients treated at level 1 centres than in level 2 and level 3 centres.

The analysis of the data obtained from the patients included in clinical trials showed a similar tendency to those seen in the studies carried out in the oncology area abroad, in which age is described as an important factor when determining whether to include patients in a clinical trial.^{35,36} In the data presented here, 6.3% of patients \leq 65 years were included in clinical trials, as opposed to 2.7% of patients >65 years (*P*=.003).

The cost study shows, on the one hand, that the costs associated with the treatment of breast cancer are extensive and that there are variations, according to the intention of the treatment, linked to the regimens used, as well as the geographical area where the treatment was administered. As we have already discussed above, at the time the study was conducted, the group of patients presenting the greatest costs associated with cytostatics was the one receiving chemotherapy for metastatic disease, but it is hoped that, as new drugs are included in the standard treatments for patients with the disease in the less advanced stages, that these differences will become smaller. Trastuzumab in the early stages is one example of this (subsequent to the gathering of the data).

The study has several limitations. Although it offers us an image of the systemic treatment of BC in our country, this is only partial, as the data was only gathered from the centres with GEDEFO representatives and participation was voluntary. The sample of participating centres was large, and although the majority of centres which treat the largest number of patients in each of the autonomous regions represented were included, the same cannot be guaranteed in terms of the smaller centres. There may possibly be a variable of confusion with regard to this classification, which would have an impact on the cost endpoint as well as that for including subjects in clinical trials. Neither was information gathered about hormone treatments, which are very important in some patient groups, especially the elderly, nor oral cytostatics (capecitabine and vinorelbine), unless these were administered combined with other intravenous drugs. Also, it must be taken into account that the costs were calculated based on the RRP. This may not accurately reflect the true situation, as the final cost of the medications depends on the procurement policies at the centres. In spite of this, and although the study design does not allow us to guarantee this, it is believed that the differences observed with regard to the cost of cytostatics in the treatment of breast cancer in the different autonomous regions represented would be related to the variations in the drugs used rather than cost differences.

The study data gives us a snapshot of the real situation of CT treatment of breast cancer in Spain and its associated costs. Future studies will enable us to understand the evolution of the treatments over time as new research contributes new scientific tests.

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The following pharmacists, listed in alphabetical order, have participated in this study:

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