The cost of breast cancer adjuvant chemotherapy in a district of Lombardy, Italy
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The cost of breast cancer adjuvant chemotherapy in a district of Lombardy, Italy

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ABSTRACT

AIMS

Literature describing the cost of adjuvant chemotherapy (ACT) in early stage breast cancer (BC) patients in Italy is scarce. This study was aimed to estimate BC ACT cost in a large district of Lombardy Region.

METHODS

A single-center, retrospective, observational study was conducted on resource consumption data (type and frequency) from the Audit System on Quality of Breast Cancer Treatment database of the San Matteo Hospital, Pavia. It included female patients with estrogen receptor-positive/human epidermal growth factor receptor 2-negative BC, resected and treated with ACT between 01/01/2012 and 01/06/2014. Exclusion criteria included metastatic disease (M1 according to TNM staging system), in situ BC, HER2 positivity. Type of treatment was based on national guidelines. The study was conducted in the perspective of regional healthcare service and therefore only included direct medical costs of ACT: chemotherapy.

ABSTRACT

OBIETTIVO

Le evidenze di letteratura italiana sul costo della chemioterapia adiuvante nel trattamento precoce del tumore della mammella sono limitate. Lo scopo del presente studio è quello, pertanto, di stimare il costo della chemioterapia adiuvante nel trattamento del tumore della mammella in Lombardia.

METODI

È stato condotto uno studio osservazionale retrospettivo monocentrico, presso il Policlinico San Matteo di Pavia, tramite la consultazione del database SQTM. Sono state incluse pazienti con tumore della mammella, con positività al recettore degli estrogeni (ER+) e negatività per il recettore di crescita epidermico (HER-), sottoposte ad un intervento chirurgico e successivamente trattate con chemioterapia adiuvante tra il 01/01/2012 e il 01/06/2014. Sono state escluse, invece pazienti in fase metastatica, (M1 secondo la stadiazione TNM), con tumore in situ e positività per HER. Lo studio è stato condotto nella prospettiva del pagatore, ovvero della Regione.
(CT), hormonotherapy (HT), radiotherapy (RT), follow-up visits and emergency room accesses were estimated, based on drugs, setting of care and DRG-based hospital reimbursements.

RESULTS

116 patients were included in the study: 36 patients received CT, 16 HT, 22 CT + HT, 17 HT + RT and 25 CT+HT+RT. The net cost associated with CT, was estimated based on the difference in average costs between subgroups 1/ CH+HT & HT and 2/ CT+HT+RT & HT+RT; and ranged from 5,975 € to 6,454 €.

CONCLUSIONS

Despite the introduction of generic drugs, the cost of CT for the National Health System (NHS) remains high. The use of genomic testing to predict benefit of CT could allow significant cost savings.

KEYWORDS

cost therapy, adjuvant chemotherapy, breast cancer

Lombardia e pertanto sono stati inclusi solo i costi diretti sanitari: chemioterapia (CT), ormonoterapia (HT), radioterapia (RT), visite di follow-up e accessi al pronto soccorso. Il consumo di risorse è stato ricavato dal database SQT M, mentre i costi unitari sono stati stimati utilizzando le tariffe regionali ospedalieri e di specialistica ambulatoriale come proxy dei costi unitari.

RISULTATI

Nella nostra indagini si è incluso 116 pazienti: 36 avevano ricevuto la CT, 16 la HT, 22 la CT + HT, 17 la HT + RT e 25 CT+HT+RT. Il costo netto associato alla CT, stimato come differenza tra il costo medio dei sottogruppi CH+HT vs HT e CT+HT+RT vs HT+RT, è risultato compreso tra 5,975 € e 6,454 €.

CONCLUSIONI

Il costo della CT per il Servizio Sanitario Nazionale (SSN) è ancora elevato, nonostante l’introduzione dei farmaci generic. È il possibile utilizzo di test genetici per selezionare i pazienti che effettivamente traggono beneficio dalla CT potrebbe consentire di ottenere risparmiati per il SSN.

SPELL OUT

AC  Adonubicin, Cyclophosphamide
ACT  Adjuvant chemotherapy
BC  Breast cancer
CMF  Cyclophosphamide, Methotrexate, 5-Fluorouracil
CRF  Case Report Form
CT  Chemotherapy
DRG  Diagnosis Related Groups
EC  Epirubicin, Cyclophosphamide
ER  Estrogen receptors

FEC  5-Fluorouracil, Epirubicin, Cyclophosphamide
HER2  Human epidermal growth factor receptor 2
HT  Hormonotherapy
LVI  Lymphovascular invasion
NHS  National Health System
PR  Progesterone receptors
RT  Radiotherapy
SQT M  Quality of Breast Cancer Treatment
INTRODUCTION

Breast cancer is the second most common malignancy in the world and the most frequent among women, with an estimated 1.67 million new cases diagnosed in 2012 (25% of all cancers). In Italy, it has been estimated that approximately 48,000 new cases of breast cancer are diagnosed every year. Its incidence shows a marked difference across the Nation, with 118.5/100,000 cases in the North, 103.5/100,000 in Central Italy and 94.4/100,000 in the South. In Lombardy, a Northern Region, 9,930 incident cases were estimated in 2014.2

Prognosis, survival and recurrence rates can vary widely, depending on a number of factors including disease stage at diagnosis and presence of molecular markers such as the estrogen and progesterone receptors (ER and PR, respectively) and the human epidermal growth factor receptor 2 (HER2). Decision on whether to use adjuvant chemotherapy (CT) in patients with early, invasive, operable breast cancer has traditionally relied on clinical, pathologic and biological markers.3

Although it is recognized that CT, after complete surgical resection confers survival advantages, current estimates indicate that more than half of patients with hormone receptor-positive breast cancer receive adjuvant CT, but less than 10%, are likely to benefit from it.4,5

In addition, anxiety is especially prevalent in women undergoing CT,6 which impacts on professional life and, consequently, on work productivity.7

A further factor needs to be added to the global burden of breast cancer management: the cost of CT. A PubMed search over the last five years literature on this subject indicated that there is a paucity of recent data on breast cancer costs, particularly on the burden of chemotherapy. A French study designed to estimate resource use and costs associated with the current standard of care for adjuvant CT for breast cancer in non-metastatic patients showed that the costs of adjuvant chemotherapy are substantial (mean cost 15,740 €/patient from a societal perspective): the main components of total cost were the cost of chemotherapy agents (26%), lost productivity (27%), chemotherapy administration (19%), and management and prevention of adverse events (16%).8

Chemotherapy-based regimens were associated with increased resource utilization (managing side effects; concomitant targeted therapy use; and increased frequencies of hospitalizations, provider visits, and monitoring tests) in a European study across 5 countries (France, Germany, The Netherlands, Belgium, and Sweden). In fact, hormone therapy is recommended as adjuvant therapy and is viewed as standard of care for hormone-receptor-positive advanced breast cancer, but the value of adjuvant chemotherapy in this setting is not well defined as well as guidelines indications. This impact resulted in a direct cost difference between chemotherapy-based and hormone therapy-based regimens approximately equal to 1,900 € to 2,500 € per month.9

The burden of cost of chemotherapy is relevant also in the American health-care system: a 2012 study examined the differences between breast cancer patients who received chemotherapy and those who did not in costs and survival by age, treatment, and axillary node status. A cohort of 23,110 node-positive and 31,572 node-negative women (aged 65 years and older, Medicare data) was used to demonstrated that the regression-adjusted difference in the average lifetime cost estimates for all node-positive patients receiving chemotherapy was approximately 2,438 $ and was significantly higher (P < 0.05) than for patients not receiving chemotherapy.10

Cost of treatments increase in case of metastatic breast cancer: an incidence-based cost of illness American model demonstrated that treatment-related costs (active treatment, toxicity management, and medical follow-up) contributed 44% of expenditure, followed by palliative/best supportive care costs (31%).11

A literature search has indicated that, to date, there are no published cost analyses stratified by patients' tumor biology, despite well-established over-treatment with chemotherapy in certain sub-groups.12 One such subgroup is that with estrogen receptor positive (ER posi-
tive) and Human Epidermal Growth Factor Receptor 2 negative (HER2 negative) disease, where the number of patients receiving chemotherapy is likely to decrease in coming years with the introduction of modern molecular testing.\(^{5,12,18}\)

Giving the lack of publications on cost of chemotherapies and other treatments in the management of breast cancer in the Italian context, this study aimed at investigating them in the clinical practice of a large district of the Lombardy region, Pavia.

As recommended by scientific societies (European Society of Breast Cancer Specialists, EUSOMA, Forza Operativa Nazionale sul Carcinoma Mammario, FONCaM, etc.), at the Breast Unit of IRCCS San Matteo Hospital Foundation, the Audit System on Quality of Breast Cancer Treatment (SQTM) is used to ensure quality in the management of breast diseases and to facilitate the monitoring of breast cancer diagnosis, treatment and follow-up.

**METHODS**

**STUDY DESIGN**

A regional, single-center, retrospective, observational study was conducted using resource consumption data (type and frequency) from the SQTM database. The study was conducted using the perspective of third-party payer, represented by the Regional Health System of Lombardy.

**DATA SOURCE AND STUDY POPULATION**

Based on clinician input, a protocol and a Case Report Form (CRF) for data collection were drafted and submitted to the local Ethics Committee for approval. Data on resource consumption was collected in this manner and then costs were appraised by using the relevant regional tariffs or published drugs cost, updated to January 2016. All clinical data were coded to protect patient confidentiality. Female patients with no metastatic and no \textit{in situ}\textsuperscript{ER+}/HER2- breast cancer, who had undergone surgical resection and treated in the timeframe between January 1\textsuperscript{st} 2012 and June 1\textsuperscript{st} 2014 were included in the study. Exclusion criteria comprised patients with metastatic (M1 according to TNM staging system) and \textit{in situ} breast cancer, HER2+ patients and patients with missing data. Data collection was performed between 01/06/2015 and 30/09/2015.

Patient characteristics, e.g. age at diagnosis, and tumor features including size, grade, morphology, the presence of lymph vascular invasion (LVI), lymph node status and final pathological stage were collected.

**COST OF ADJUVANT THERAPY**

According to the adopted perspective, the analysis comprised direct medical costs of treatment during the first year after surgery, i.e. adjuvant CT, hormonotherapy (HT) and radiotherapy (RT), in addition to follow-up visits and possible visits to emergency room due to the management of therapy side effects.

The cost of adjuvant CT included the cost of drug schemes (Table 1), concomitant medications provided to prevent side effects (Table 2) and outpatient stay, appraised according to the Diagnosis Related Groups (DRG) 410 tariff (CT without secondary diagnosis of acute leukemia fee Hospital Discharge Form for reimbursement of the drug through files F, 4700 €).

The cost of HT combined the cost of prescribed drugs (Table 3) and that of the intervention of preventive ovariectomy according to DRG 355 tariff (operations on the uterus and annexes for cancer not correlated to ovarian adnexal without complications, 4,567 €).

The cost of RT was represented by that of irradiation of one or more sites among breast, chest and supraclavicular area. The cost of each irradiation was estimated using the regional fees for outpatient services and ranged from 1,957.19 € of chest irradiation to 6,619.84 € of breast irradiation.

The follow-up costs included the cost of specialist consultations and of diagnostic and laboratory tests, estimated using regional tariffs. A first multidisciplinary visit and subsequent oncologic visits were considered
TABLE 1
Chemotherapy schemes and related average costs

<table>
<thead>
<tr>
<th>Chemotherapy scheme</th>
<th>Drugs</th>
<th>Dosage and schedule</th>
<th>Number of cycles</th>
<th>Average cost* (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>Doxorubicin 60 mg/mq iv, day 1, every 21 days</td>
<td>4</td>
<td></td>
<td>2,619.00</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide 600 mg/mq iv, day 1, every 21 days</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Taxol 80 mg/mq iv, every week</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMF</td>
<td>Cyclophosphamide 100 mg/die per os, days 1-16, every 28 days</td>
<td>12</td>
<td></td>
<td>115.00</td>
</tr>
<tr>
<td></td>
<td>Methotrexate 40 mg/mq iv, days 1-8, every 28 days</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-Fluorouracil 600 mg/mq iv, days 1-8, every 28 days</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEC</td>
<td>5-Fluorouracil 500-600 mg/mq iv, day 1, every 21 days</td>
<td>6</td>
<td></td>
<td>540.00</td>
</tr>
<tr>
<td></td>
<td>Epirubicin 75-100 mg/mq iv, day 1, every 21 days</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide 500-600 mg/mq iv, day 1, every 21 days</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EC</td>
<td>Epirubicin 90 mg/mq iv, day 1, every 21 days</td>
<td>4</td>
<td></td>
<td>319.00</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide 600 mg/mq iv, day 1, every 21 days</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Without considering the multiplication by the body surface area or kg; AC: Doxorubicin, Cyclophosphamide; iv: intravenous; CMF: Cyclophosphamide, Methotrexate, 5-Fluorouracil; FEC: 5-Fluorouracil, Epirubicin, Cyclophosphamide; EC: Epirubicin, Cyclophosphamide.

TABLE 2
Costs of drugs administered for prophylaxis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and schedule</th>
<th>Average cost* (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>12 mg before each cycle</td>
<td>1.70</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>8 mg before each cycle</td>
<td>5.70</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 mg before each cycle</td>
<td>0.43</td>
</tr>
<tr>
<td>G-CSF*</td>
<td>500,000 unit/kg/die for 10 days after each cycle</td>
<td>10.311</td>
</tr>
<tr>
<td>Prednisone*</td>
<td>75 mg before taxol dose</td>
<td>0.50</td>
</tr>
<tr>
<td>Clodronamine*</td>
<td>5 vials 1 ml/10 mg</td>
<td>9.90</td>
</tr>
</tbody>
</table>

* Per cycle; *Assumption: G-CSF is given only as secondary prophylaxis in 10% of patients treated with FEC and in 5% of patients treated with AC; *before taxol dose.

TABLE 3
Cost of hormone therapy drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Reference price (£)</th>
<th>Price per mg (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>20 mg/die</td>
<td>4.58</td>
<td>0.011</td>
</tr>
<tr>
<td>Letrozol</td>
<td>2.5 mg/die</td>
<td>66.66</td>
<td>0.881</td>
</tr>
<tr>
<td>Anastrozol</td>
<td>1 mg/die</td>
<td>35.80</td>
<td>1.279</td>
</tr>
</tbody>
</table>

for all patients. Other specialist consultations include psychologist, physiotherapist, and gynecologist and radiologist consultations. Emergency costs, based on the triage method which applies a color code according to the severity of event, included the cost of each visit to the emergency room due to breast cancer diagnosis and related therapies, such as earache and intolerance (white code, 41.32 £), thrombosis, edema, pain, dizziness and blood disorders (green code, 156.94 £), breast inflammation and drug poisoning (yellow code, 309.87 £).

STATISTICAL ANALYSIS

Descriptive statistical analysis were performed, frequency and percentage were reported for the categorical variables while mean and standard deviation (SD) for continuous variables.

Given the lack of assumption in this cost analysis and only relation between the resource consumption, derived by SGTM database, and the unit costs, derived by National Tariff, any sensitivity analysis was performed.


COST OF ADJUVANT THERAPY

The average annual direct costs per patient by treatment group are summarized in Figure 2 and detailed below.

**Group A - Adjuvant CT**

CT only as adjuvant therapy after surgery was prescribed to 36 patients, distributed as follows: 30 women received doxorubicin and cyclophosphamide (AC) followed by taxol, 1 cyclophosphamide, methotrexate and 5-fluorouracil (CMF), 2 5-fluorouracil, epirubicin and cyclophosphamide (FEC) and 3 epirubicin and cyclophosphamide (EC). The average CT cost was 6,986±1,911 €, which included the cost of drugs, prophylaxis and administration.

The average total annual direct cost per patient treated after surgery with CT only was 7,520±1,940 €, 93% of which were due to CT, and the remaining 7% due to follow-up (Figure 2).

**Group B - HT**

16 patients were prescribed HT only as adjuvant therapy after surgery. One patient underwent ovariectomy. The remaining 15 patients were administered HT drugs (letrozole in 6 cases, anastrozole in 5 and tamoxifen in 4).

The average total annual direct cost per patient was 787±1,085 €, which decreased to 518 € (47.5% of which [i.e. 246 €] due to drug cost) after excluding the ovariectomized patient.

**Group C - CT-HT**

22 patients were treated with both CT and HT. As for HT, only 1 patient underwent ovariectomy, while the remaining 21 received HT drugs (8 tamoxifen, 7 anastrozole and 6 letrozole). Excluding the ovariectomized patient, the average cost for HT drugs was 206 €.

Regarding CT, 9 patients were treated with AC, 2 with CMF, 7 with FEC and 4 with EC. The mean cost for CT drugs was 5,813±2,816 € (which included the cost of drugs, prophylaxis and administration).

The average annual direct cost per patient in group C was 6,762±2,605 €, of which 86% depended on CT, 7.5% on follow-up, 6% on HT, and 0.5% on emergency costs.

**Group D - HT+RT**

17 patients (mean age: 61 years) received HT and RT following quadrantectomy. Three patients underwent ovariectomy and 16 were administered HT drugs (7 tamoxifen, 7 anastrozole and 2 letrozole).
REFERENCES


19. Diaby, V., et al., A review of systematic reviews of the cost-effectiveness of hormone therapy, chemotherapy-
RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

The final sample included 116 patients (Figure 1), treated for breast cancer, after breast surgery and in the reference period, who were sub-grouped based on the type of therapy prescribed: adjuvant CT only, Group A; HT only, Group B; CT+HT, Group C; HT+RT, Group D; CT+HT+RT, Group E.

As recommended by national guidelines, the decision on the type of treatment to prescribe was mainly based on prognostic factors, as: histopathological tumor grading (I-III), cancer stages, hormone receptor status, HER 2 status, proliferative activity, age and comorbidities. Histopathological grade III indicates a poor prognosis, while grade II is more difficult to interpret and often a reclassification to grade I or III occurs after genetic profile analysis. The proliferative activity is measured by the Ki-67 score, which allows distinguishing between breast cancer subtype luminal A or luminal B/HER2- in ER+ and/or PgR+ and HER2- patients. According to the 2013 St. Gallen Consensus Conference, the 20% cut off in the Ki-67 score distinguishes luminal A from luminal B, while according to 2009 St. Gallen Consensus Conference the cut off is set at 14%. Luminal A, ER+ and/or PgR+ and HER2- patients are usually treated with HT only, while luminal B patients benefit from the addition of adjuvant CT to HT, as the prognosis is worse.

As shown in Table 4, reporting the histopathological tumor grading and proliferative activity, patients administered HT alone (group B) or HT+RT (group D) mainly had a good prognosis, whereas those prescribed CT alone (group A) or CT+HT (group C) or CT+HT+RT (group E) had a dismal prognosis. Indeed, tumor grading was I in 75% (12/16) of subjects in group B and 100% (17/17) in group D, and the Ki-67 score was <15% in 75% (12/16) and 88.2% (15/17), respectively. On the contrary, tumor grading was III in 58.3% (21/36), 54.5% (12/22) and 32% (8/25) of patients included in group A, C and E, respectively, and the Ki-67 score was >15% in 75% (21/36), 81.8% (18/22) and 60% (15/25) of patients in group A, C and E, respectively.

FIGURE 1
Characteristics of the study population

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients included</th>
<th>N=116</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>CT</td>
<td>N=36</td>
</tr>
<tr>
<td>Group B</td>
<td>HT</td>
<td>N=16</td>
</tr>
<tr>
<td>Group C</td>
<td>HT+CT</td>
<td>N=22</td>
</tr>
<tr>
<td>Group D</td>
<td>HT+RT</td>
<td>N=17</td>
</tr>
<tr>
<td>Group E</td>
<td>HT+CT+RT</td>
<td>N=25</td>
</tr>
</tbody>
</table>

TABLE 4
Patient distribution across therapy group by nodal stage and Ki-67 score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
<th>Group E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0 (0)</td>
<td>12 (75)</td>
<td>0 (0)</td>
<td>17 (100)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>II</td>
<td>15 (41.7)</td>
<td>3 (18.8)</td>
<td>10 (45.5)</td>
<td>0 (0)</td>
<td>16 (64)</td>
</tr>
<tr>
<td>III</td>
<td>21 (58.3)</td>
<td>0 (0)</td>
<td>12 (54.5)</td>
<td>0 (0)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>N.A.</td>
<td>0 (0)</td>
<td>1 (6.2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ki-67 score (%)</td>
<td>0-5</td>
<td>3 (8.3)</td>
<td>5 (31.2)</td>
<td>1 (4.5)</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td></td>
<td>6-16</td>
<td>6 (16.7)</td>
<td>7 (43.8)</td>
<td>3 (13.7)</td>
<td>9 (52.9)</td>
</tr>
<tr>
<td></td>
<td>15-30</td>
<td>15 (41.7)</td>
<td>4 (25)</td>
<td>17 (77.3)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td></td>
<td>&gt;30</td>
<td>12 (33.3)</td>
<td>0 (0)</td>
<td>1 (4.5)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Data are expressed as frequencies (n, %): CT: chemotherapy; HT: hormone therapy; RT: radiotherapy; N.A.: not available.
Group C (HT+CT) and between Group D (HT+RT) and Group E (HT+RT+CT), the difference is completely attributed to CT and follow-up, and indeed it is very close to the cost of CT of Group A (CT).

The different costs increase when CT is administered. Therefore, avoiding regimens with CT in favor of HT alone when possible and indicated may provide a benefit for patients in terms of health and safety concerns, and for the health care system, as the economic burden would decrease.

A number of studies have examined the cost-effectiveness of one or more drugs used in the treatment of BC, while only little evidence is available from specifically on the cost of total treatment in the BC. Three studies have investigated the cost of some cancers, included the BC, finding that the cost of CT, similarity to the present one, is the main driver of total cost.

A study carried out in Spain investigated the total cost of BC for stage of tumour, including also the cost of diagnosis. The authors have estimated that the cost of treatment (update to 2011) was 9,838 €, 17,270 €, 22,145 € and 28,776 € while the cost of follow-up was 172 €, 908 €, 994 € and 1,166 €, respectively for stage 0, I, II and III.

Others two studies conducted in France evaluated the cost of CT in Metastatic BC. The first study compared two groups of patients treated in different period, one between the 1994 and 1998 and the other between 2003 and 2006. The average cost per patient (update to 2008) was 6,272 € for the first group (1994-1998) and 13,035 € for the other one (2003-2006). The second one, estimated that the average CT cost per patients, on a group of 371 patients treated during the period ranged on 2001 to 2006, was 3,919 € (+-8,049 €).

At our best knowledge, this is the first study to provide information on the alternative treatment options in place in Italy for female patients with no metastatic and no in situ ER+/HER2- breast cancer, who have undergone surgical resection, as well as on the direct costs that the Italian NHS sustains for these patients.

Its findings highlight for Italian NHS which are the most figures and drivers of costs in BC. We think that this information is important especially in the light of novel tools that are going to be implemented in the management of breast cancer patients, able to help clinicians in taking evidence-based decisions.

Once these tools are available, an economic assessment will help defining them not only clinically, but also economically in terms of real impact on NHS budget.

Despite highlighting data on the cost of alternative treatment for no metastatic and no in situ ER+/HER2- breast cancer, the main limitation of this observational study is the small sample size, due to monocentric study, that can results in a constraint on findings generalizability.

In addition this small sample not ensure the representativeness of Italian populations.

As data were collected from existing clinical database, this study relies on available data on resource consumption while the data on unit cost analysis was based on Regional tariff rather than on productivity cost. Moreover the SQTM database doesn’t include the adverse events monitoring, except for emergency room access.

Lastly, when comparing the average annual costs between the different groups of treatment, it must be noted that any adjusted analysis was done.

Future analysis including a larger number of centres and patients would be desirable to confirm these results.

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The total average annual direct cost per patient treated with HT+RT was €8,185±2,912. Considering the 3 ovariec- tomized patients, the average cost of HT was €964±1,767, whereas, excluding ovariec- tomy costs and considering only HT drugs, the average cost decreased to €173. RT cost depends almost entirely on the cost of breast irradiation (€6,619 per patient). In fact, 16/17 patients received breast irradiation only, while 1 patient received irradiation for 2 sites (supraclavicular area and breast).

**Group E** - CT+HT+RT

25 patients were treated with CT+HT+RT. For these patients, therapy was stronger due to the more severe clinical features depending on invasiveness and staging of the tumour (Table 4). 19 patients (mean age: 59 years) underwent quadrantectomy.

Regarding HT costs, within this group only 1 patient underwent ovariectomy, while the remaining 24 were administered HT drugs (11 letrozole, 8 tamoxifen and 5 anastrozole). Excluding ovariectomy, the average cost for HT drugs in this group was €243.

With regard to CT, 13 patients received AC followed by taxol, 4 CMF, 7 FEC and 1 EC, with an average cost of €6,248±2,564.

As for RT, the average cost was higher in group E because 8 patients received irradiation to more than one site (3 sites in 1 case and 2 sites in 7).

The total average annual direct cost per patient treated with CT+HT+RT was €14,639±3,784, 51% of which represented by RT, 43% by CT and 3% by HT.

**COST DIFFERENCES AMONG TREATMENT GROUPS**

The difference in the total average annual direct cost per patient among groups of treatment was calculated by comparing the group not receiving CT with the related group administered CT. The differential cost between group B (HT) and group C (HT+CT) was €5,975, and between group D (HT+RT) and group E (HT+RT+CT) was €6,654, solely related to CT and follow-up costs (Figure 2). No significant differences in emergency visits were observed, indicating a correct use of concomitant medications provided to prevent side effects in all subgroups.

Considering patients groups where CT is administered (CT, HT+CT, HT+RT+CT), the average cost of CT (weighted for the relative proportion of patients in each group) was €6,452. Considering Group A as a benchmark, these results fit with the assessed average annual cost of CT of €6,986.

Considering the HT groups (HT, HT+CT, HT+RT, HT+RT+CT), the weighted average cost of HT was €549 and, excluding the cases of ovariectomy, the total cost was €220.

**COST OF FOLLOW-UP BY GROUP AND TYPE OF TREATMENT**

Although the patient flow chart for breast cancer is well established by procedures in force at IRCCS San Matteo, the cost of follow-up showed some differences among the 5 groups of treatment, which were related to individual clinical variability. The main differences were observed in the follow-up of CT (A, C and E; 521±169, 512±147 and 551±147, respectively) versus non-CT groups (B and D; 261±109 and 234±176, respectively), while no relevant difference existed among single groups, among CT groups and among non-CT groups. The estimated difference in the average cost of follow-up depended specifically on the percentage of patients who were visited by an oncologist and by the annual number of oncological visits.

**DISCUSSION**

The results of the present study provide a plausible estimation of the direct medical costs of ER+/HER2- patients who have undergone breast surgery, and have received adjuvant therapy as one of the following five possible options: CT, HT, HT+ CT, HT+RT and CT+HT+RT.

The main difference among groups depends on the administration of adjuvant CT, and the high cost of treatment of patients undergoing CT compared to those receiving HT is mostly due to the cost of chemotherapy.

When comparing the cost between Group B (HT) and