Neoadjuvant treatment for locally advanced breast cancer. Comparison of two schemes based on docetaxel-epirubicin vs. 5-fluorouracil-epirubicin-cyclophosphamide

Ana Olivia Cortés-Flores,* Gilberto Morgan-Villéla,** Juan Manuel Castro-Cervantes,** Gonzalo Vázquez-Camacho,*** Clotilde Fuentes-Orozco,* and Alejandro González-Ojeda*

Abstract

Background: Breast cancer is the most common type of cancer in women worldwide. In Mexico, >34% of patients are in locally advanced stages at the time of diagnosis. Neoadjuvant chemotherapy is administered to control local disease, make surgical resection possible and increase the possibility of breast tissue conservation.

Methods: We performed a double-blind, randomized clinical trial in patients with locally advanced breast cancer (stages IIB and IIIA) with two therapy schemes; 5-fluorouracil-epirubicin-cyclophosphamide (control group) vs. docetaxel-epirubicin (study group). Both were indicated in three preoperative cycles, and patients were submitted afterwards to surgery. Pathological response was measured.

Results: Forty one patients were included in our study. They were distributed in two homogeneous groups: 21 in the control group and 20 in the study group. Dimensional pathological response was higher in the study group than in the control one (p <0.05). Five patients in the control group and ten patients of the study group experienced complete pathological response (p <0.05). The most common secondary events were leucopenia, neutropenia and fever. Morbidity, number of lymph nodes, disease-free survival and general survival did not show significant differences between groups. No mortality was reported during a minimum follow-up of 28 months.

Conclusions: Our results confirm the effectiveness of docetaxel-epirubicin to obtain complete pathological response. Neoadjuvant therapy has been shown to increase the pathological response when a taxane is added to an anthracycline. This combination presented more secondary events, but they can be effectively managed medically. Neoadjuvant docetaxel-epirubicin followed by surgery is an appropriate regimen for patients with locally advanced breast cancer.

Key words: neoadjuvant chemotherapy, breast cancer.

Resumen

Introducción: El cáncer de mama es la neoplasia más común en mujeres en el mundo. En nuestro país, hasta 34% de las pacientes se encuentran en etapas localmente avanzadas al momento del diagnóstico. La quimioterapia preoperatoria favorece el control local de la enfermedad, la convierte en operable y aumenta la posibilidad de conservación mamaria.

Material y métodos: Ensayo clínico, con asignación al azar, doble ciego en cáncer de mama localmente avanzado (estadios clínicos IIB y IIIA), en dos brazos de tratamiento, el primero a base de 5-fluorurocil-epirubicina-ciclofosfamida, y el segundo docetaxel-epirubicina. Ambos esquemas se indicaron en 3 ciclos preoperatorios, posteriormente las pacientes fueron sometidas a cirugía y se midió la respuesta patológica en la pieza quirúrgica.

Resultados: Se estudiaron 41 pacientes las cuales fueron distribuidas en dos grupos; 21 pacientes en el grupo control y 20 pacientes en el grupo de estudio. La respuesta patológica dimensional presentó diferencia a favor del grupo experimental. Cinco casos del grupo control y 10 del experimental tuvieron respuesta patológica completa (p <0.05). Los efectos adversos significativos fueron leucopenia, neutropenia y fiebre. La morbilidad, el número de ganglios, la sobrevida libre de enfermedad y la sobrevida general, no mostraron diferencias significativas entre grupos. No se ha presentado mortalidad a un mínimo de 28 meses de seguimiento.

Conclusiones: Nuestros resultados favorecen al grupo tratado con docetaxel-epirubicina en términos de respuesta patológica, lo cual concuerda con lo descrito en estudios previos realizados con la misma combinación. Aunque se presentaron mayor número de efectos adversos en el grupo de estudio, éstos pueden ser controlados con manejo médico. El uso de antraciclinas añadas con taxanos ha demostrado tener mejores resultados respecto al uso de otras combinaciones. Esto fortalece el establecimiento de esta combinación como primera línea de tratamiento en pacientes con cáncer de mama en etapas IIB y IIIA.

Palabras clave: quimioterapia neoadyuvante, cáncer de mama.
Introduction

Breast cancer is the most common malignant neoplasia affecting women in developed countries. In Mexico, breast cancer is the second most frequent neoplasia after cervico-uterine cancer. Between 25,000 and 30,000 new cases are diagnosed annually.\textsuperscript{1,2}

It is less frequent to detect locally advanced breast cancer in developed countries where only 10 to 20% cases are reported. In developing countries, incidence of breast cancer is between 30 and 60%\textsuperscript{3}. Surgical resection is the principal treatment in patients with breast cancer. Surgery and/or postoperative radiotherapy may control local and regional disease in the majority of patients. However, treatment results in patients with locally advanced disease are generally poor. In general, these results improve significantly with the development of chemotherapy. Neoadjuvant or preoperative treatment allows conversion of some cases of inoperable breast cancer to a treatable disease by means of surgical resection.\textsuperscript{4} Multidisciplinary therapy is now the treatment of choice for patients with locally advanced breast cancer. This provides adequate local control, possibility of breast conservation, and increase in patient survival.\textsuperscript{3}

Observations of improvement of survival after administration of adjuvant chemotherapy suggest that administration of chemotherapy with primary treatment could minimize the emergence of chemoresistant clones and therefore reduce or eradicate metastatic disease. The reasons for preoperative chemotherapy are based on the potential clinical benefit, increase in the resectability of the tumor and reduction of size of the primary tumor, thereby improving local control of the disease and allowing breast preservation surgery.

The resurgence in the 1900s of new and powerful drugs, in particular paclitaxel and docetaxel, brought about the urgency of the process of pharmacological development. It has taken approximately 10 years to reach the understanding of how taxanes could be sequentially used and in combination with anthracyclines could improve the prognosis of patients with advanced disease.\textsuperscript{5}

The present study compares two pre-operative chemo-therapeutic techniques, docetaxel-epirubicin vs. 5-fluorouracil-epirubicin-cyclophosphamide, in patients with locally advanced breast cancer where complete pathological response was our variable of highest response.

Materials and Methods

Patients

We performed a double-blind, random selection, controlled clinical trial. Included in the study were those patients between the ages of 18 and 60 years with histologically or cytologically confirmed breast adenocarcinoma in stages IIb and IIIa (tumors T3, N0, N1, N2 and large T2 tumors in proportion to the size of the breast) without previous oncological treatment. All patients had a Karnofsky index >70% and adequate hematological, renal and hepatic function and were without evidence of metastatic disease. All patients were evaluated with a complete physical examination. Other diagnostic tests included chest x-ray, abdominal echosonography and bone scan. Computerized axial tomography was done only when patients presented with intracranial manifestations.

Treatment

The first treatment scheme (study group) consisted of administration of docetaxel (80 mg/m\textsuperscript{2}) and epirubicin (80 mg/m\textsuperscript{2}), whereas the second scheme (control group) consisted of 5-fluorouracil (500 mg/m\textsuperscript{2}), epirubicin (80 mg/m\textsuperscript{2}) and cyclophosphamide (500 mg/m\textsuperscript{2}). Both treatments were each administered for 3 weeks for a total of three cycles, with the prior administration of dexamethasone (16 mg), ranitidine (100 mg) and ondansetron (8 mg), and after the chemotherapy received antiemetic prophylaxis with S-HT3 antagonist receptors.

All patients were subjected to surgery during a period not longer than 6 weeks after the conclusion of chemotherapy, once normal hematological biometric values returned to normal levels. Surgeries were radical modified mastectomy or breast conservation surgery according to clinical response (>50% were candidates for conservation surgery) and were always performed by the same surgical oncologist. Surgical specimen was sent to the pathologist who evaluated lymph node status and pathological response.

Consolidation chemotherapy was initiated at a minimal interval of 6 weeks after surgery. The treatment scheme was administered each 21 days over four to six cycles, depending on the pathological response obtained with neoadjuvant therapy. A complete cycle of chemotherapy was indicated in patients who had conservation surgery and was initiated immediately after surgery. In patients who had modified radical mastectomy, radiotherapy was indicated after consolidation chemotherapy.

Clinical evaluation was made at the end of each cycle. Toxicity was evaluated each week and recorded in each cycle. Determinations of hemoglobin, neutrophils and platelets were done each week. Hepatic, renal and cardiovascular functions were monitored at the end of each cycle of neoadjuvant chemotherapy by means of hepatic function tests that included liver enzymes, bilirubin levels, serum protein (albumin and globulin) and prothrombin time. For renal function, uric levels, creatinine and serum uric acid levels were determined, and for monitoring of cardiovascular function the patients were clinically evaluated. If cardiotoxicity was suspected, a cardiology evaluation was requested, which included an electrocardiogram and/or echocardiogram, if necessary.

Patients had an open appointment to the emergency department of the institution if necessary and investigators provided telephone support 24 h/day.
Evaluation of Response

The primary objective of the study was the evaluation of response rates to neoadjuvant chemotherapy. Patients were evaluated if and when they received the three planned cycles of chemotherapy. Clinical response of the tumor was performed bi-dimensionally using mammography and clinical measurement of the tumor. Clinical response was any decrease in the original dimension of the tumor in relationship to the baseline. Pathological response was measured on the surgical sample postoperatively. Complete pathological response was seen as a microscopic disappearance of the tumor on the surgical specimen.

Statistical Analysis

Results were expressed as proportions, measures of central tendency and dispersion. For the inferential phase, results were analyzed using \( \chi^2 \) test or Fisher’s exact test in case of dichotomous variables or proportions and by Student’s t-test. Values of \( p < 0.05 \) were considered statistically significant.

Table 1. Descriptive statistics of the clinical characteristics of the patients

<table>
<thead>
<tr>
<th>Number of patients by group</th>
<th>Control ((n = 21))</th>
<th>Study ((n = 20))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(^{a})</td>
<td>52.5 ± 8.29</td>
<td>49.1 ± 8.4</td>
</tr>
<tr>
<td>Initial tumor size(^{a}) (cm)</td>
<td>37 ± 26</td>
<td>37 ± 30</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>IIIA</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Laboratory determinations(^{b})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.8 ± 1.5</td>
<td>13.6 ± 1.2</td>
</tr>
<tr>
<td>Leukocytes (cells/cc)</td>
<td>7276.2 ± 1762.4</td>
<td>6345.0 ± 1506.6</td>
</tr>
<tr>
<td>Neutrophils (cells/cc)</td>
<td>4307.9 ± 1314.3</td>
<td>3996.2 ± 1083.2</td>
</tr>
<tr>
<td>Platelets (cells (\times 10^3/\text{ml}))</td>
<td>271.8 ± 77.6</td>
<td>271.9 ± 60.2</td>
</tr>
<tr>
<td>Estrogen receptors ((n)^{c})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Negative</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Progesterone receptors ((n)^{c})</td>
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<td></td>
</tr>
<tr>
<td>Positive</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Negative</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Her2Neu receptors ((n)^{c})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Negative</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>p53 receptors ((n)^{c})</td>
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<tr>
<td>Positive</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Negative</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

\(^{a}\)Mean ± SD.

\(^{b}\)Hemoglobin in g/dL, leukocytes, neutrophils and platelets \(10^9/\text{L}\).

\(^{c}\)Two patients of the study group and two patients of the control group did not have receptor determinations performed due to complete pathological response of the surgical specimen and because preoperative material was not satisfactory for performing labeling techniques.

Ethical Considerations

The study protocol was approved by the Local Committee of Health Investigations (registration #2002/252/131 and Ethics Committee (#179/03/19). All patients who agreed to participate in the study signed informed consent. The authors declare that they do not have any conflict of interest. Adverse events were recorded daily and the local committees were informed in a timely manner of the presence of each of them. Up until January 17, 2005 there were 41 patients who received three cycles of neoadjuvant chemotherapy and were surgically intervened. Minimum follow-up was 28 months and maximum was 44 months.

Results

From September 2003 to January 2005, there were 41 patients included in the study. Twenty patients comprised the study group with 21 patients in the control group. Median age was 52.5 ± 8.29 years for the control group and 49 ± 8.41 years for the experimental
group. Initial size of the tumor of the control group was 37 ± 26 cm, and in the experimental group tumor size was 37 ± 30 cm ($p = 0.968$). Table 1 demonstrates the descriptive statistics of the groups for age, initial size of the tumor, hemoglobin, leukocytes, neutrophils and platelets on admission to the study.

Pathological response was analyzed in both treatment groups to identify the distribution of the results. Baseline tumor size was similar in both groups but not the final size of the tumor, finding a statistically significant difference between groups, favoring the study group where the dimensions of the tumor were reduced significantly. Mean and standard deviation for the control group was 11.3 ± 14.89 cm and for the experimental group was 4.25 ± 7.79 cm ($p = 0.037$). Complete pathological response was reported in five (23.8%) cases of the control group and in 10 (55.5%) cases of the experimental group, with a statistically significant difference ($p = 0.042$) (Figure 1).

Toxicity secondary to the chemotherapy was studied. The most common laboratory alteration was myelotoxicity in both groups. Leukopenia, neutropenia and thrombocytosis were the alterations that showed a significant difference in some determinations of the experimental group. We did not observe thrombocytopenia in any of the groups. There was no difference in hemoglobin between groups during the neoadjuvant course of treatment.

Other adverse events were alopecia, nausea, vomiting, diarrhea, stomatitis, fever, headache, constipation and herpes zoster infection. There was no significant difference between groups with the exception of fever associated with neutropenia, which was more frequent in the experimental group because 20% of the patients developed it. Only one patient required hospital management associated with dehydration. Granulocyte colony-stimulating factor (Filgastrim) was used to treat patients in the experimental group who had neutropenia (4/20). There was no case of hepatic, renal or cardiac toxicity. There was no mortality associated with the chemotherapeutic schemes.

Postoperative morbidity was reported for a patient from the experimental group who presented partial necrosis of the adipocutaneous flap, and the incidence of seromas was 18 and 20%, respectively. There was no significant difference in the frequency of postoperative complications and there was no mortality related to the procedure.

During histopathological evaluation, the number of metastatic lymph nodes of breast adenocarcinoma involved in the axillary region obtained during surgery was studied (Figure 2). Proportion of conservative procedures and modified radical mastectomy did not show significant differences between groups. Twenty five percent of the control group patients and 35% of the study group patients were subjected to breast conservation surgery ($p = 0.4$).

Regarding biological markers, estrogen and progesterone, P53 and Her2neu, determination was performed by immunohistochemistry with the anatomic tissue used for histopathological study. There was no material to stain for these receptors in two control group patients and in two patients from the experimental group due to a complete pathological response of the surgical specimen and because the preoperative material was not satisfactory to perform these staining techniques (Figure 3).

During the follow-up, two patients from the control group presented local recurrence of the disease (10.5%). Both were Her2neu positive vs. no patients from the experimental group, although one patient from the experimental group had progression due to cerebral and pulmonary metastases and was also Her2neu positive (5%). The difference between disease-free patients until the dates previously mentioned is not statistically significant.

All patients were still alive as of April 2007.

**Figure 1.** Complete pathological response. Percentage of pathological response observed in control (23%) and experimental (56%) groups. $P^*$ with $\chi^2$ test.

**Figure 2.** Lymph node behavior in surgical sample. No difference was observed between control and experimental group with regard to lymph node number.
Discussion

Unfortunately, in Mexico the majority of patients diagnosed with breast cancer are in locally advanced stages. This is precisely the focus of this study, which was performed with the goal of comparing two regimens of neoadjuvant chemotherapy in patients with these characteristics, thereby evaluating clinical response and pathology. Neoadjuvant chemotherapy has been changed in the standard treatment of patients with tumors ≥3 cm and in locally advanced breast cancer T3, T4 or N2. Its administration has been popularized when its safety and efficacy have been confirmed through important prospective and controlled studies, systematic revisions and meta-analysis.

The principal objective of the docetaxel-epirubicin combination is to increase the possibility of breast conservation therapy and to increase the clinical and pathological response. For many years, the cyclophosphamide, methotrexate and 5-FU regimen (CMF) was used with good results. Subsequently, the advantage of anthracyclines over methotrexate was demonstrated and the chemotherapeutic schemes were modified to cyclophosphamide, Adriamycin, or epirubicin and 5-FU (FAC or FEC). At 5 years, the difference in disease-free, recurrence and survival favors the regimens that contain anthracyclines (57% vs. 54%, p = 0.006) and 72% vs. 69% (p = 0.02), respectively.

Combination schemes with doxorubicin and cyclophosphamide have been used with 80% clinical rates of response (complete clinical response of 36% and pathological response of 9%). In a controlled study, after preoperative therapy with four cycles of doxorubicin and cyclophosphamide, 80% of the patients demonstrated a reduction of at least 50% in tumor size, and 36% presented complete clinical response.

Of the new agents commercialized in recent years, docetaxel is one of the most active in breast cancer. Combination of docetaxel with doxorubicin is one of the strongest options that can be tried as neoadjuvant chemotherapy in locally advanced breast cancer.

Docetaxel is at present the reference drug for the treatment of breast cancer. In Europe and in other countries as well, it actually constitutes the first line of treatment with the advantage of being able to be combined with other products without increasing toxicity. The combination of docetaxel plus doxorubicin is feasible, safe and highly active.

Nabholtz and Riva compared docetaxel against mitomycin + vinblastine in patients with metastatic breast cancer, finding docetaxel significantly superior in terms of response (30 vs. 11.6%, p = 0.0001), average time of progression of the disease (19 vs. 1 week, p = 0.001), and survival (11.4 vs. 8.7 months, p = 0.0097).

Chan et al. performed a comparative study of docetaxel vs. doxorubicin in patients with metastatic breast cancer, finding that docetaxel presents a significantly greater rate of objective responses than doxorubicin (47.8 vs. 33.3%, p = 0.008).

De Matteis used docetaxel + epirubicin neoadjuvantly in locally advanced breast cancer. This author reports 76.7% of objective clinical responses, of which 20% were complete clinical responses. There was complete pathological response in 13.3% of the cases. In our study, complete pathological response and reduction in tumor size favored the study group, as shown in our results.

Studies have also been performed where docetaxel was primarily used with results of 67% partial response and 18% complete response. Other reports suggest up to 40% of objective responses in metastatic disease with anthracyclines, which increased to 60% or more with the use of anthracyclines combined with taxanes with a response of ~8 months duration (range 3-16 months) and an average time of progression of 4.5 months. Two-year survival was 60%.

Sjostrom et al. made a comparative study between doxorubicin plus taxane vs. a regimen containing anthracyclines (5-FU, anthracyclines and cyclophosphamide) in patients with metastatic breast cancer. Their results demonstrated that the response rate with doxorubicin + placitaxel was significantly greater than with 5-FU, anthracyclines and cyclophosphamide (68 vs. 55%, p = 0.032) and disease-free survival was greater (average 8.3 vs. 6.2 months, p = 0.034). Survival was greater in patients treated with paclitaxel + doxorubicin (22.7 months) than in those treated with FAC (18.3 months), with a significant difference (p = 0.02). Similarly, the number of cycles the patients were subjected to has been compared with combinations of anthracyclines and taxanes. The greater number of cycles (from four to six) has demonstrated a significant increase in the complete pathological response compared with those patients who have been subjected to two or three cycles.

Adverse effects, although mild, were greater in our study group. Monitoring of toxicity and medical management controlled these events, for which this combination can be administered with safety and with mild adverse effects.
Pathological status of axillary lymph nodes in patients with breast cancer after neoadjuvant chemotherapy has shown a correlation in terms of prognosis and disease-free survival. Tumor excision is considered possible in 86% of patients with T1 tumors, 70% with T2 tumors T2 and 3% of T3 tumors. Breast conservation is significantly greater in patients subjected to neoadjuvant chemotherapy, ~25% of the patients with locally advanced disease. There was no pattern observed in improvement of the pathological response based on determinations of receptors for estrogen, progesterone, p53 and Her2Neu. Other studies have demonstrated a greater range of response in those patients with estrogen-receptor-positive tumors.

Use of neoadjuvant epirubicin and docetaxel proved to be more effective, well tolerated, and highly active compared with the 5-FU-epirubicin-cyclophosphamide scheme. Neoadjuvant therapy with anthracyclines and taxanes, followed by surgical resection, proved to have highly favorable results. If adverse events were reported, they did not progress to more serious life-threatening consequences. Therefore, it is proposed as an active regimen for the neoadjuvant management of locally advanced breast cancer.

Acknowledgments

This project was supported by the program “Seminario de Metodología Aplicada a la Investigación en Salud (Lectura crítica aplicada a la literatura médica)”, Coordinación de Investigación en Salud, Delegación Jalisco del IMSS, Guadalajara, Jalisco, Mexico.

Conflict of interest statement:
The authors declare that they do not have any conflict of interest.

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