Neoadjuvant Chemotherapy for Breast Cancer and the Impact of Pathologic Complete Response

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Abstract

Introduction: Neoadjuvant chemotherapy for breast cancer over the last several years is being utilized with increasing frequency. Neoadjuvant therapy can potentially downstage advanced regional disease, increasing the likelihood of negative surgical margins. This study analyzes the utilization and outcomes of neoadjuvant chemotherapy for breast cancer at a single institution.

Methods: A retrospective chart review was performed at the Jacqueline M Wilentz Breast Center in Long Branch, New Jersey. All patients from 2010 to present that underwent neoadjuvant chemotherapy for breast cancer were analyzed. The initial biopsy pathology, initial staging workup, response to therapy, operation, surgical pathology reports were studied. Chi square analysis was then used to identify factors more likely to yield a pathologic complete response. Finally, outcomes in patients that did and did not have a pathologic complete response were examined.

Results: The most common indications for neoadjuvant therapy for advanced regional disease and Her2 positive status. The tumor was successfully downstaged in 29 of 46 patients (63.0%), with 13 (28.3%) achieving pathologic complete response. The major predictors of pathologic complete response were chemotherapy regimen and Her2 status, as 12 of 21 patients (57.1%) patients with amplified Her2 and 8 of 12 (66.7%) patients receiving TCHP therapy achieving pCR. Predictive factors of residual disease included triple negative status and treatment with ACT chemotherapy. Pathologic complete response was predictive of favorable prognosis, as no patient that achieved a pCR had recurrence, local or distant, within the time frame of this study. Factors predictive of recurrence included residual nodal disease or residual tumor T3 or greater.

Conclusion: In our retrospective study, neoadjuvant chemotherapy successfully downstages patients in the majority of patients. The patients that were able to derive the most benefit from neoadjuvant therapy were those with Her2 amplified tumors, and those that underwent therapy with TCHP. Achievement of pCR incured a favorable prognosis.

Keywords: Neoadjuvant Chemotherapy; Breast Cancer

Introduction

Neoadjuvant chemotherapy (NAC) is becoming increasingly utilized in the treatment of invasive breast cancer. This therapy has classically been utilized in advanced local disease,[1] and more recently has been used to increase the likelihood of breast conservation and negative nodal disease [2, 3]. Even more recent is the use of NAC in the treatment of early stage breast cancer in an effort to treat the systemic aspects of disease prior to surgery [4]. One of the potential positive outcomes from NAC is attaining a pathologic complete response (pCR), defined as no remaining tumor on pathologic assessment. Studies have suggested that obtaining a pCR after NAC portends a favorable prognosis, with improved disease free survival rates [5, 6]. In this study, a retrospective review of patients undergoing NAC at a community institution was analyzed. The aim of this study was to identify trends in the utilization of NAC in a community setting as well as factors that may contribute to achieving a pCR. The response of the primary tumor and the outcomes of patients receiving NAC was also examined.

Materials and Methods

After obtaining appropriate Institutional Review Board approval, ICD-10 and CPT codes were used to identify all patients that had received NAC at Jacqueline M. Wilentz Breast Center since 2010. These charts were then examined for patient demographic data, initial staging workup, chemotherapy regimen, post-neoadjuvant staging, surgery performed, pathology reports, and follow up. With this information, rates of tumor and axillary response were examined along with patient outcomes, with attention paid to those with pCR. Chi square analysis and Fisher exact test was then utilized to determine if certain tumor characteristics or certain chemotherapy regimens were more likely to predict a pCR. Outcomes were then analyzed to determine if pCR, among other factors, was predictive of improved disease free survival.

Results

Forty six patients were identified that met study criteria. The average age of patients receiving chemotherapy was 54.4
years, and all patients were female. 42.1% of patients had a family history of breast cancer, and 27.7% of patients underwent genetic testing. No patients tested positive for BRCA. 42.6% of patients had a history of smoking. Demographic data is outlined in Table 1.

Initial average primary tumor size was 4.9 centimeters. According to the TNM staging classification, 8 (17.4%) patients had T1 tumors, 14 (30.4%) patients had T2 tumors, 13 (28.2%) patients had T3 tumors, and 11 (23.9%) patients had T4 tumors. Of those with T4 tumors, 2 had inflammatory breast cancer. 29 (63.0%) patients had nodal disease at time of diagnosis. 45 of 46 patients had invasive ductal cancer, with the one remaining having invasive lobular carcinoma. 27 (58.7%) patients were hormone positive, 22 (47.8%) patients had amplified Her2, and 9 (19.6%) patients were triple negative. Average Ki67 was 49%, ranging from 10-90%. Histological data is outlined in Table 2.

Chemotherapeutic regimens are outlined in Table 3. The majority of patients were treated either with ACT (Adriamycin, Cyclophosphamide, Taxol) or TCH (Taxotere, Carboplatin, Herceptin). In more recent years of the study, pertuzumab was added to the TCH regimen (TCHP). There were 24 (52.2%) patients that underwent treatment with ACT, and 4 (8.7%) patients had Herceptin added to ACT for Her2 positivity. Five (10.9%) patients underwent treatment with TCH, and in more recent years 13 (28.2%) patients underwent treatment with TCHP.

After completion of NAC, patients underwent definitive surgery. Nine (19.6%) patients underwent breast conserving surgery with lumpectomy and sentinel lymph node biopsy, 4 (8.7%) patients underwent a lumpectomy with axillary lymph node dissection, 18 (39.1%) patients underwent mastectomy with sentinel lymph node biopsy, and 15 (32.6%) patients underwent modified radical mastectomy. Surgical data is outlined in Table 4.

On pathologic analysis, 34 (73.9%) patients demonstrated regression of the primary tumor. Of the 29 patients that initially had node positive disease, 13 (44.8%) patients remained node positive, leaving 16 (55.2%) patients node negative. 2 (4.3%) patients demonstrated progression of disease, with pathologic analysis revealing nodal disease not present on initial assessment. Pathologic complete response was achieved in 13 (28.3%) patients. Of these 13 patients, 8 were treated with TCHP, 2 with ACT, 1 with ACTH, and 2 with TCH.

Table 4 outlines factors predictive of pathologic complete response. Initial tumor characteristics, treatment regimens and extent of surgery was evaluated using chi square analysis. Her2 positive disease and treatment with TCHP were found to be factors predictive of pCR. Triple negative disease and treatment with ACT were found to be predictive of residual disease.

The average follow up period of the study was 39.5 months. 32 (69.6%) patients are currently disease free, including all 13 patients that achieved a pathologic complete response. 14 patients (30.4%) experienced a recurrence, 10 are deceased and 4 are alive with disease. Average disease free survival in patients that had a recurrence was 24 months, and 13 of 14 patients had a recurrence within 3 years.

Table 6 outlines factors predictive of tumor recurrence. Initial tumor characteristics, extent of surgery and pathologic characteristics were examined using chi square analysis. Factors predictive of tumor recurrence included bulky residual tumor (T3 or greater) and residual nodal disease. pCR was found to be protective against tumor recurrence.

Discussion

In this study, patients receiving NAC were analyzed over the past seven years at a single institution. NAC has been
Table 5: Factors that influence pathologic complete response.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pathologic Complete</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Response</td>
<td></td>
</tr>
<tr>
<td>Tumor Size (cm)</td>
<td>Yes (n=13)</td>
<td>No (n=33)</td>
</tr>
<tr>
<td>Initial Nodal Disease</td>
<td>4.36</td>
<td>5.21</td>
</tr>
<tr>
<td>Hormone Positive</td>
<td>7 (53.8%)</td>
<td>20 (60.6%)</td>
</tr>
<tr>
<td>Her2 Amplified</td>
<td>6 (46.2%)</td>
<td>21 (63.6%)</td>
</tr>
<tr>
<td>Triple Negative</td>
<td>12 (92.3%)</td>
<td>10 (30.3%)</td>
</tr>
<tr>
<td>Ki67 (mean)</td>
<td>0.0%</td>
<td>27.3%</td>
</tr>
<tr>
<td>Treatment with ACT</td>
<td>1 (7.7%)</td>
<td>23 (69.7%)</td>
</tr>
<tr>
<td>Treatment with ACTH</td>
<td>2 (15.4%)</td>
<td>3 (9.1%)</td>
</tr>
<tr>
<td>Treatment with TCH</td>
<td>2 (15.4%)</td>
<td>3 (9.1%)</td>
</tr>
<tr>
<td>Treatment with TCHP</td>
<td>8 (61.5%)</td>
<td>4 (12.1%)</td>
</tr>
<tr>
<td>Breast Conserving Surgery</td>
<td>5 (38.5%)</td>
<td>8 (24.2%)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>8 (61.5%)</td>
<td>25 (75.8%)</td>
</tr>
</tbody>
</table>

Table 6: Factors that influence tumor recurrence.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Recurrence</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Size (cm)</td>
<td>Yes (n=14)</td>
<td>No (n=32)</td>
</tr>
<tr>
<td>Initial nodal disease</td>
<td>5.92</td>
<td>4.13</td>
</tr>
<tr>
<td>Hormone Positive</td>
<td>9 (64.3%)</td>
<td>18 (56.3%)</td>
</tr>
<tr>
<td>Her2 Amplified</td>
<td>3 (21.4%)</td>
<td>19 (59.4%)</td>
</tr>
<tr>
<td>Triple Negative</td>
<td>4 (28.6%)</td>
<td>3 (9.4%)</td>
</tr>
<tr>
<td>Ki67 (mean)</td>
<td>48.20%</td>
<td>46.50%</td>
</tr>
<tr>
<td>Breast Conserving Surgery</td>
<td>3 (21.4%)</td>
<td>10 (31.3%)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>11 (78.6%)</td>
<td>22 (68.7%)</td>
</tr>
<tr>
<td>Residual tumor T3 or greater</td>
<td>8 (57.1%)</td>
<td>8 (25%)</td>
</tr>
<tr>
<td>pCR</td>
<td>6 (42.9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>0 (0%)</td>
<td>13 (40.6%)</td>
</tr>
</tbody>
</table>

The data from the present study reinforce the information from these studies. There was no significant difference in local-regional recurrence in patients that underwent breast conserving surgery when compared to patients that underwent mastectomy. All recurrences in this study were noted to be distant, with nearly all recurrences diagnosed within three years of surgery. Predictors of recurrence in this study included residual nodal disease and large residual tumor.

When determining appropriate chemotherapy regimens for patients, selection typically depends on extent of disease at diagnosis, the histological characteristics of the tumor, and the patient’s ability to tolerate therapy. At the author’s institution, patients with non-Her2 amplified disease received ACT therapy prior to surgery. Patients with Her2 amplification received TCH. In later portions of the study, patients with Her2 amplified disease received pre-operative pertuzumab in addition to the TCH regimen. Studies have demonstrated that treatment with anthracycline based chemotherapy with docetaxel in the neoadjuvant setting improves pCR rates and decreases local recurrence [8,14]. This study demonstrated significant response to the ACT regimen in terms of regression of the primary tumor. As a result, several patients were able to undergo breast conserving surgery. However, only one patient was able to achieve pathologic complete response, and eleven of the fourteen patients that recurred were treated initially with ACT. Patients treated with ACT in this study were more likely to have larger tumors and nodal disease at time of diagnosis when compared to patients treated with other regimens.

When treating patients with Her2 positive disease, previous studies have demonstrated benefit to using trastuzumab. In the NOAH trial, patients with Her2 positive locally advanced or inflammatory breast cancer were randomized to either add trastuzumab in the neoadjuvant and adjuvant setting or no additional therapy added to their standard neoadjuvant chemotherapy regimen of doxorubicin, paclitaxel, cyclophosphamide, methotrexate, and fluorouracil. Addition of trastuzumab demonstrated improved event-free survival compared to the control group, without significant cardiotoxicity [15].

More recently, the addition of pertuzumab to the above regimen was studied to determine if there was added benefit in the neoadjuvant setting. As pertuzumab and trastuzumab both carry risk of cardiotoxicity, the TRYPHAENA study aimed to determine if pertuzumab could safely be added to a regimen consisting of trastuzumab. The results of this study demonstrated the safety of this combination [16]. Pertuzumab has previously been demonstrated to show benefit in patient with metastatic Her2 positive breast cancer, as evidenced by the results of the CLEOPATRA trial. In this trial, patients with first line metastatic Her2 positive breast cancer were randomized to receive either pertuzumab, trastuzumab and docetaxel or placebo, trastuzumab and docetaxel. Over a median follow up of 30 months, the addition of pertuzumab demonstrated significant improvement in progression free and overall survival without undue toxicity [17].

demonstrated to be equivalent to adjuvant therapy in terms of disease free and overall survival [7,8]. One of the tenets of neoadjuvant therapy is to give patients the opportunity to undergo breast conserving therapy who would have otherwise required a mastectomy. Previous studies have demonstrated that those patients that undergo breast conserving therapy have equivalent outcomes to those patients that undergo mastectomy when controlled for stage [9,10]. This appears to hold true for patients that become candidates for breast conserving therapy after NAC who would have otherwise needed a mastectomy. Select patients that undergo breast conserving surgery after NAC have local disease recurrence rates similar to those that undergo mastectomy [11,12]. A study out of M.D Anderson identified predictors of local-regional recurrence and ipsilateral breast tumor recurrence including advanced nodal involvement at diagnosis, residual tumor >2 cm, residual multifocal disease and lymphovascular invasion [13].
With the results of the CLEOPATRA study, a more recent study examining pertuzumab with trastuzumab in the neoadjuvant setting was examined in the Neosphere trial. On initial phase II analysis, patients were randomized to four separate groups to receive trastuzumab with docetaxel, pertuzumab with docetaxel, trastuzumab and pertuzumab with docetaxel, or trastuzumab and pertuzumab without docetaxel. Patients receiving all three therapies demonstrated significantly improved pathologic complete response rates when compared to other groups (45.8%), and adverse events between all groups were similar [18]. In the five year follow up analysis of this study, progression free and disease free survival was analyzed. After undergoing one of the four above neoadjuvant regimens and surgery, patients received 3 cycles of fluorouracil, epirubicin and cyclophosphamide and an additional 17 cycles of trastuzumab to complete a year’s worth of treatment. Results of this analysis suggested that neoadjuvant pertuzumab in addition to trastuzumab and docetaxel is beneficial, and that a pCR could be a long term indicator for Her2 positive cancer [19].

The findings of the present study support the above studies. In this study, the majority of patients that were able to achieve pCR were Her2 positive and treated with TCHP. There were no reported adverse cardiac events related to this regimen. Moreover, eight of twelve patients treated with TCHP were able to achieve pCR. It is important to note that patients receiving neoadjuvant TCHP were more likely to have early breast cancer with smaller tumors than those patients in earlier portions of the study. No patients treated with this regimen have had a recurrence. These data further support the use of TCHP in the neoadjuvant setting.

Obtaining pathologic complete response is an important predictor of outcome in patients undergoing neoadjuvant therapy. Controversy exists as to what true pCR entails. When examining existing studies in which pCR is examined, three commonly used definitions exist. ypT0 ypN0, meaning no invasive or in situ disease in the breast or axilla, ypT0 ypN0 with no invasive disease identified (meaning in situ disease only can still classify as complete response), or ypT0, meaning no invasive or in situ disease in the breast without specification of disease in the axilla. The Collaborative Trials in Neoadjuvant Breast Cancer working group performed an analysis of 12 neoadjuvant trials, and concluded that those patients that achieved the former two definitions of pCR had a stronger association with improved event free and overall survival when compared with the latter definition [20].

In the present study, pCR was defined as no residual invasive or in situ cancer on pathologic analysis (ypT0N0). Previous studies have demonstrated that pCR is associated with a good prognosis, especially in patients with aggressive subtypes [20-22, 24]. The results from this study further support pCR as an indicator of favorable prognosis. All patients that were able to achieve pathologic complete response were currently disease free, and the fourteen patients that suffered a cancer recurrence were not disease free at time of surgery. This suggests that susceptibility of a breast cancer to chemotherapy portends a good prognosis.

Some subtypes of breast cancer are more responsive to chemotherapy, and a pCR does not carry the same prognostic information across all subtypes. Patients with indolent and hormone positive breast cancers are generally not as sensitive to chemotherapy as more aggressive subtypes [23]. Additionally, patients that do not achieve a pCR in the more aggressive subtypes have a worse prognosis when compared to patients that do, which does not hold true in patients with more indolent, hormone positive cancers [24]. The findings of this study support previous literature, in that patients who underwent chemotherapy for Her2 amplified disease and triple negative disease appeared to have higher incidence of pCR. Additionally, this study reaffirms the favorable prognosis for patients with these subtypes who achieve pCR, as all patients who achieved pCR in this study are currently disease free.

After surgery, the question remains what to do next. In the aforementioned Neosphere study, patients received additional chemotherapy after completing NAC, and completed trastuzumab for a year. Patients with Her2 amplified disease in our study also received adjuvant trastuzumab for one year following surgery. In Her2-negative patients a recent study examined the use of adjuvant Capecitabine following neoadjuvant anthracycline or taxane based chemotherapy for patients with residual carcinoma. Additional therapy following surgery with Capecitabine was found to be beneficial, especially in triple negative patients, improving disease free and overall survival [25]. This study addresses the question of what to do with our patients with residual disease. Information from the present study and previous studies demonstrate poor prognosis for those patients with residual disease, and the above study aims to address this issue. Further studies are needed to elucidate optimal management of patients with residual disease after neoadjuvant therapy.

This study highlights several of the benefits of NAC in patients with breast cancer. This treatment offers an in vivo assessment of chemotherapeutic response prior to surgery, providing important prognostic information. This approach can also be used in early stage breast cancer to eliminate occult metastatic disease. Patients that seem to derive most benefit from NAC are those with more aggressive subtypes, including triple negative and Her2 amplified patients. This study and previous studies support the current interest in tailoring therapies to achieve pCR in aggressive breast cancer subtypes.

Conclusion

In this study, patients undergoing NAC for breast cancer were typically treated based on extent of disease and tumor characteristics. NAC successfully decreased tumor size, leading to the ability to perform breast conserving surgery in some cases where it may not have otherwise been feasible. Achieving pathologic complete response was indicative of favorable prognosis, as all patients that were able to achieve pCR are currently disease free. Limitations to the study include small sample size and limited follow up with patients that have more recently undergone treatment. Further studies are needed to identify optimal treatment of patients with residual disease after neoadjuvant treatment.
References


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