REVIEW

Neoadjuvant Therapy for Breast Cancer

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INTRODUCTION

Nearly all patients with advanced breast cancer will derive some benefit from systemic therapy, which in the non-metastatic setting is typically offered following surgical removal of the tumor (i.e., adjuvant therapy). However, preoperative (neoadjuvant) systemic therapy is currently preferable for patients with inoperable inflammatory or locally advanced breast cancer. A favorable clinical response to neoadjuvant therapy can convert many patients with inoperable cancers into candidates for surgical resection. For patients with operable tumors, which are large in relation to the size of the breast, breast-conserving surgical therapy (BCT) may not be feasible. In this clinical setting, neoadjuvant therapy may lead to a reduction in tumor size, which if significant, may allow consideration of BCT.

Neoadjuvant therapy initially referred to systemic chemotherapy, but in recent years endocrine therapy for tumors expressing estrogen and/or progesterone receptors has been established as a well-tolerated and effective alternative neoadjuvant strategy. Also, for patients whose tumors overexpress human epidermal growth factor receptor 2 (HER2), the targeted agent, trastuzumab, has been incorporated into neoadjuvant strategies.

In addition to the impact on the surgical options, either by facilitating BCT or by rendering a tumor operable at all, neoadjuvant therapy may provide other benefits. Although preclinical models suggested that neoadjuvant therapy might impact the biology of the tumor and improve survival outcomes compared to adjuvant therapy, this has not been demonstrated in the clinical trials. However, neoadjuvant therapy does provide an in vivo model to assess the efficacy of a specific regimen, in contrast to adjuvant therapy, for which there are no clinical markers to follow.

This article will provide a review of neoadjuvant therapy for breast cancer, including preclinical data, results of clinical trials, implications for BCT, timing of sentinel node biopsy, and the utility of magnetic resonance imaging (MRI) to predict response to therapy.


KEY WORDS: breast cancer; neoadjuvant therapy; sentinel node; MRI

PRECLINICAL CONSIDERATIONS AND DATA

Six hypotheses have been described that offer theoretical advantages to neoadjuvant over adjuvant chemotherapy:

1. Earlier initiation of systemic therapy. Neoadjuvant systemic therapy can target clinically occult micrometastases when the tumor burden of metastatic disease is potentially lower [1]. The preoperative delivery of non-cross resistant agents may minimize the development of a resistant cell population that can form from spontaneous mutations [2].

2. Reduction of microscopic tumor dissemination caused during surgical removal of tumor.

3. Prevention of tumor growth spurt after surgical resection. Studies with animal models have shown that removal of a primary tumor accelerated the growth of metastatic tumors [3,4]. This appears to be mediated by an increase in the rapidity of tumor growth in any residual tumor following removal of a tumor of the same type [5].

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Fisher et al. [6] administered cyclophosphamide to mice with two separate mammary adenocarcinoma tumor implants, prior to resection of one of these tumors. Preoperative cyclophosphamide resulted in a lower labeling index of the residual tumor when compared to postoperative cyclophosphamide. In a separate experiment, preoperative administration of the endocrine agents tamoxifen or goserelin, a luteinizing hormone-releasing hormone (LH-RH) analog, also prevented the increase in tumor growth kinetics of the distant tumor [7].

1. Delay in curative local therapy, which may allow the primary tumor to metastasize or progress to an inoperable state during the course of neoadjuvant therapy.
2. Concern for loss of accurate staging information, as many early trials noted a lack of invasive cancer in the surgical specimens of women after neoadjuvant therapy.
3. While treatment of micrometastases is generally felt to be beneficial, Skipper [9] had proposed that the primary tumor and micrometastases need not necessarily respond to the same therapy.
4. While the tumor vasculature may be intact prior to surgical resection, neoadjuvant therapy will have to treat a much greater burden of disease than if used after tumor removal.
5. Exposure to neoadjuvant therapy could promote drug resistance.
6. Increased risk of surgical or radiation complications after neoadjuvant therapy.

Theoretical disadvantages to neoadjuvant treatment include:

NEOADJUVANT CHEMOTHERAPY FOR INFLAMMATORY AND LOCALLY ADVANCED (INOPERABLE) BREAST CANCER

The term “inflammatory breast cancer” was coined by Lee and Tannenbaum [10] in 1924. They described 28 patients with breast cancer that had a unique skin involvement, in which the “skin becomes deep red or reddish purple, and to the touch is brawny and infiltrated.” This condition was further characterized in 1956 by Haagensen [11], who established the clinical criteria for the diagnosis, including rapidly enlarging breast, generalized breast induration, and erythema involving at least a third of the breast. Using current National Cancer Center Network (NCCN) criteria, inflammatory breast cancer is a clinical syndrome in women with “invasive breast cancer that is characterized by erythema and edema (peau d’orange) of a third or more of the skin of the breast and with a palpable border to the erythema [12].” Physical examination reveals an erythematous and warm breast, often in the absence of a dominant breast mass. The clinical course is more rapid than non-inflammatory breast cancer and diagnosis is often delayed, with many patients diagnosed as having breast infections prior to biopsy. The underlying biology of inflammatory breast cancer includes dermal lymphatic invasion, which accounts for its clinical presentation as well as its explosive clinical course. Most patients with inflammatory breast cancer have involvement of regional lymph nodes, and 17–36% have distant metastases at the time of diagnosis [13].

Inflammatory breast cancer is classically considered inoperable, as surgery alone has been described as ineffective, with a 5-year survival rate of less than 5% [14]. Radiation has been studied, either alone or in conjunction with surgery, but in prior clinical trials, there was no impact on the survival rates [15]. Even in the absence of locoregional failure, most patients died with distant metastases. These circumstances led to the study of systemic chemotherapy prior to surgery, which yielded dramatically better outcomes. A retrospective analysis of 50 patients with inflammatory breast cancer found that patients treated with chemotherapy, radiotherapy, and surgery had a better 5-year survival rate than patients who did not receive all three modalities (50% vs. 7%) [16]. Inflammatory breast cancer is relatively uncommon, which explains the relative paucity of data from large trials. With few exceptions, patients with inflammatory breast cancer are treated in trials for patients with locally advanced breast cancer, as both of these groups fare poorly with locally directed therapies.

Locally advanced breast cancer is loosely defined but typically includes patients with clinical stage IIIb and IIIc breast cancer, though some clinicians would also include clinical stage Iib and IIIa. Some of the characteristics of locally advanced breast cancer include a tumor size greater than 5 cm (T3), skin or chest wall involvement (T4), matted axillary lymph nodes (N2), or involvement of the internal mammary, infraclavicular or supraclavicular lymph nodes. For these patients, treatment with surgery and radiation can offer local control, but survival is still poor because the most common type of treatment failure is distant metastatic disease. This led to the study of neoadjuvant chemotherapy for patients with both inflammatory and locally advanced breast cancer. No randomized trials have compared neoadjuvant and adjuvant chemotherapy for these patients, in part because many surgeons consider these tumors inoperable prior to chemotherapy. In general, these studies have shown that neoadjuvant chemotherapy is tolerable and significantly improves outcomes compared to surgery alone. As a result of these studies (Table I), patients with inflammatory and locally advanced breast cancer receive neoadjuvant chemotherapy as part of standard treatment, though no standard regimen has been established.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>Population</th>
<th>Chemotherapy regimen</th>
<th>pCR rate</th>
<th>Overall RR</th>
<th>5-year DFS</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hortobagyi et al. [66]</td>
<td>1988</td>
<td>174</td>
<td>LABC</td>
<td>FAC</td>
<td>16.7%</td>
<td>NR</td>
<td>84% (for IIIa), 33% (for IIIb)</td>
<td>84% (for IIIa), 44% (for IIIb)</td>
</tr>
<tr>
<td>Perloff et al. [67]</td>
<td>1988</td>
<td>113</td>
<td>LABC and IBC</td>
<td>CAFVP</td>
<td>NR</td>
<td>72%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pierce et al. [68] and Low et al. [69]</td>
<td>1992, 2004</td>
<td>107</td>
<td>LABC and IBC</td>
<td>CAFM</td>
<td>29%</td>
<td>57%</td>
<td>NR</td>
<td>61% (for IIIa), 36% (for IBC), 31% (for non-IBC IIIb)</td>
</tr>
<tr>
<td>Colozza et al. [70]</td>
<td>1996</td>
<td>31</td>
<td>LABC and IBC</td>
<td>CAP</td>
<td>8%</td>
<td>76.7%</td>
<td>29% (6 years)</td>
<td>28% (6 years)</td>
</tr>
<tr>
<td>Ueno et al. [71]</td>
<td>1997</td>
<td>172</td>
<td>IBC</td>
<td>FAC, FACVP, FACVP ± MV</td>
<td>NR, NR, NR</td>
<td>74%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Clark et al. [72]</td>
<td>1998</td>
<td>34</td>
<td>LABC</td>
<td>A</td>
<td>21%</td>
<td>65%</td>
<td>77% (3 years)</td>
<td>88% (3 years)</td>
</tr>
<tr>
<td>Cristofanilli et al. [73]</td>
<td>2001</td>
<td>42</td>
<td>IBC</td>
<td>FAC</td>
<td>12%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Smith et al. [28] and Hutcheon et al. [75]</td>
<td>2002</td>
<td>50, 47</td>
<td>LABC</td>
<td>CVAP, CVAP + docetaxel</td>
<td>16%, 34%</td>
<td>66%, 94%</td>
<td>77% (3 years), 90% (3 years)</td>
<td>84% (3 years), 97% (3 years)</td>
</tr>
<tr>
<td>Harris et al. [76]</td>
<td>2003</td>
<td>54</td>
<td>IBC</td>
<td>CMF or FAC</td>
<td>30%</td>
<td>52%</td>
<td>49%</td>
<td>56%</td>
</tr>
<tr>
<td>McIntosh et al. [77]</td>
<td>2003</td>
<td>166</td>
<td>LABC</td>
<td>CVAP</td>
<td>15%</td>
<td>75%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ezzat et al. [80]</td>
<td>2004</td>
<td>126</td>
<td>LABC</td>
<td>PC</td>
<td>16%</td>
<td>91%</td>
<td>63%</td>
<td>85%</td>
</tr>
<tr>
<td>Gajdos et al. [81]</td>
<td>2004</td>
<td>138</td>
<td>LABC</td>
<td>CMF orCAF</td>
<td>13%</td>
<td>53%</td>
<td>46%</td>
<td>55%</td>
</tr>
<tr>
<td>Lebowitz et al. [82]</td>
<td>2004</td>
<td>30</td>
<td>LABC</td>
<td>Docetaxel + capecitabine</td>
<td>10%</td>
<td>90%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>de Matteis et al. [83]</td>
<td>2004</td>
<td>30</td>
<td>LABC + IBC</td>
<td>ET</td>
<td>13.3%</td>
<td>76.7%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Shen et al. [84]</td>
<td>2004</td>
<td>33</td>
<td>LABC + IBC</td>
<td>NR</td>
<td>12%</td>
<td>85%</td>
<td>70%</td>
<td>78%</td>
</tr>
<tr>
<td>Thomas et al. [30]</td>
<td>2004</td>
<td>193</td>
<td>LABC</td>
<td>VACP</td>
<td>12.2%</td>
<td>83.4%</td>
<td>51%</td>
<td>60%</td>
</tr>
<tr>
<td>Erol et al. [85]</td>
<td>2005</td>
<td>74</td>
<td>LABC</td>
<td>CMF</td>
<td>18.9%</td>
<td>88%</td>
<td>52%</td>
<td>79.9%</td>
</tr>
<tr>
<td>Gradishar et al. [86]</td>
<td>2005</td>
<td>45</td>
<td>LABC</td>
<td>Docetaxel</td>
<td>10%</td>
<td>49%</td>
<td>NR</td>
<td>80%</td>
</tr>
<tr>
<td>Kao et al. [87]</td>
<td>2005</td>
<td>15</td>
<td>LABC and IBC</td>
<td>T + vinorelbine + XRT</td>
<td>46.7%</td>
<td>93%</td>
<td>33% (4 years)</td>
<td>56% (4 years)</td>
</tr>
<tr>
<td>Tham et al. [88]</td>
<td>2005</td>
<td>51</td>
<td>LABC</td>
<td>Docetaxel</td>
<td>20%</td>
<td>75%</td>
<td>NR</td>
<td>72% (2 years)</td>
</tr>
<tr>
<td>Veyret et al. [89]</td>
<td>2006</td>
<td>102</td>
<td>IBC</td>
<td>FEC-HD</td>
<td>14.7%</td>
<td>91.1%</td>
<td>35.7% (10 years)</td>
<td>41.2% (10 years)</td>
</tr>
<tr>
<td>Ellis et al. [27]</td>
<td>2006</td>
<td>265</td>
<td>LABC and IBC</td>
<td>AC + T, metronomic AC + T</td>
<td>17%, 26%</td>
<td>NR, NR</td>
<td>NR, NR</td>
<td>NR, NR</td>
</tr>
<tr>
<td>Villman et al. [90]</td>
<td>2008</td>
<td>41</td>
<td>LABC and IBC</td>
<td>ECX</td>
<td>19%</td>
<td>74%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>von Minckwitz et al. [91]</td>
<td>2008</td>
<td>1390</td>
<td>LABC and IBC</td>
<td>TAC</td>
<td>22.2%</td>
<td>100%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Manga et al. [92]</td>
<td>2009</td>
<td>60</td>
<td>LABC and IBC</td>
<td>ATX</td>
<td>8.3%</td>
<td>77%</td>
<td>76% (3 years)</td>
<td>90% (3 years)</td>
</tr>
</tbody>
</table>

RR, response rate; DFS, disease-free survival; OS, overall survival; IBC, inflammatory breast cancer; LABC, locally advanced breast cancer; NR, not reported; XRT, radiation therapy; CAFVP, cyclophosphamide + doxorubicin + fluorouracil + vincristine + prednisone; FAC, fluorouracil + doxorubicin + cyclophosphamide; VP, vincristine + melphalan; CMF, cyclophosphamide + methotrexate + 5-fluorouracil; CAF, cyclophosphamide + doxorubicin + 5-fluorouracil; MV, methotrexate + vinblastine; FEC, 5-fluouracil + epirubicin + cyclophosphamide; A, doxorubicin; AC, doxorubicin + cyclophosphamide; T, paclitaxel; CAP, cyclophosphamide + doxorubicin + cisplatin; CAEM, cyclophosphamide + doxorubicin + 5-fluorouracil + methotrexate; CVAP, cyclophosphamide + vincristine + doxorubicin + prednisone; ET, epirubicin + docetaxel; PC, paclitaxel + cisplatin; VACP, vincristine + doxorubicin + cyclophosphamide + prednisone; AT, doxorubicin + docetaxel; EC, epirubicin + cyclophosphamide; CEF, cyclophosphamide, + epirubicin + fluorouracil; TAC, docetaxel + doxorubicin + cyclophosphamide.
A high clinical response rate but lack of survival benefit was demonstrated in a randomized trial by Makris et al. [19]. In this study, initially reported by Powles et al. [20], patients with operable breast cancer were randomized to receive preoperative (neoadjuvant) or postoperative (adjuvant) chemotherapy. Patients received either mitomycin + mitoxantrone + methotrexate (3M) or mitoxantrone + methotrexate (2M). Patients in the adjuvant arm received eight cycles, and those in the neoadjuvant arm received four cycles prior to surgery and four cycles following surgery. Neoadjuvant therapy was associated with a pathologic complete response rate of 18%, and 89% of patients were eligible for BCT (77% were eligible prior to treatment). There was no significant difference in disease-free or overall survival rates between the neoadjuvant and adjuvant arms. However, if neoadjuvant therapy were relatively much less efficacious than adjuvant therapy, it would be difficult to discern differences in survival rates between the two regimens [21].

In the subsequent NSABP B-18 trial, patients received either neoadjuvant or adjuvant chemotherapy after being stratified by age, tumor size, and clinical node status [22]. Patients in the neoadjuvant arm did not receive any chemotherapy after surgery, regardless of response of the tumor to primary chemotherapy. This study randomized 1,523 patients with operable invasive breast cancer to four cycles of preoperative versus postoperative doxorubicin and cyclophosphamide (AC) chemotherapy plus tamoxifen (if >50 years of age). Of the 683 patients who received preoperative chemotherapy, 36% had a clinical complete response and 9% achieved a pathologic complete response. The breast conservation rate in the group receiving preoperative chemotherapy (67%) was significantly higher than in the group receiving postoperative chemotherapy (60%; P = 0.002). There was no difference in the overall or disease-free survival rates between the two groups. But a subset analysis demonstrated that those with pathologic complete responses after preoperative chemotherapy had significantly improved overall and disease-free survival rates than those with pathologic incomplete responses to preoperative treatment. In addition, the rate of BCT was related to initial tumor size. So, only 20% of those presenting with an initial tumor >5 cm and having preoperative chemotherapy were able to have breast conservation.

The benefit of incorporating a taxane into therapy was demonstrated in the NSABP B-27 trial, which examined the role of docetaxel (T) following neoadjuvant AC [23]. In this study, 2,411 patients with operable invasive breast cancer were randomized to one of the three treatment arms: (1) neoadjuvant AC followed by surgery; (2) neoadjuvant AC followed by T and then surgery; or (3) neoadjuvant AC followed by surgery and then T. The addition of T did not significantly improve disease-free or overall survival rates, despite the fact that the pathologic complete response rate (25.6%) was twice that in NSABP B-18 (13.7%). In addition, the lumpectomy rate did not significantly differ between the treatment arms of AC alone (61%) versus AC followed by T (63%; P = 0.70). Based primarily on these data, neoadjuvant therapy became widely accepted not only for those who desired BCT but were not eligible based on initial tumor size and adjuvant chemotherapy were able to have breast conservation.

A meta-analysis by Mauri et al. [24] included nine randomized studies that compared neoadjuvant therapy with adjuvant therapy, regardless of regimen and local therapy. The analysis did not detect significant differences between the two treatment regimens in mortality, disease progression, or distant recurrence rates. Neoadjuvant therapy was associated with an increased risk of loco-regional recurrence compared to adjuvant therapy. It is noted that a portion of patients receiving neoadjuvant therapy had only primary radiation for local control, whereas those receiving adjuvant therapy all had surgical resection. The conclusion from the meta-analysis was that neoadjuvant and adjuvant chemotherapy had equivalent rates of survival and disease progression (Table II).

### Table II. Trials Comparing Neoadjuvant and Adjuvant Chemotherapy for Operable Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>Chemotherapy regimen</th>
<th>BCT rate</th>
<th>DFS</th>
<th>Overall RR</th>
<th>BCT rate</th>
<th>DFS</th>
<th>Overall RR</th>
<th>BCT rate</th>
<th>DFS</th>
<th>Overall RR</th>
<th>BCT rate</th>
<th>DFS</th>
<th>Overall RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonadonna et al. [18]</td>
<td>1990</td>
<td>165</td>
<td>Neoadjuvant CMF, neoadjuvant FAC, neoadjuvant FEC</td>
<td>4.2%</td>
<td>77%</td>
<td>77%</td>
<td>81%</td>
<td>61%</td>
<td>6%</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Scholl et al. [93,94] and Broet et al. [95]</td>
<td>1995, 1999</td>
<td>200, 190</td>
<td>Neoadjuvant FAC, adjuvant FAC</td>
<td>NR, N/A</td>
<td>65%, N/A</td>
<td>65%, N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bear et al. (B-27) [23]</td>
<td>2006</td>
<td>768, 767, 776</td>
<td>Neoadjuvant AC, neoadjuvant FAC, neoadjuvant FAC</td>
<td>12%, 6%, 6%</td>
<td>28%, 14%, 14%</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bear et al. [16]</td>
<td>1998</td>
<td>160</td>
<td>Neoadjuvant FAC, adjuvant FAC</td>
<td>15%</td>
<td>73%</td>
<td>73%</td>
<td>73%</td>
<td>73%</td>
<td>73%</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bear et al. [16]</td>
<td>2000</td>
<td>134</td>
<td>Neoadjuvant FAC, neoadjuvant FAC</td>
<td>14%</td>
<td>73%</td>
<td>73%</td>
<td>73%</td>
<td>73%</td>
<td>73%</td>
<td></td>
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</tr>
<tr>
<td>Bear et al. [16]</td>
<td>2001</td>
<td>134</td>
<td>Neoadjuvant FAC, neoadjuvant FAC</td>
<td>13%</td>
<td>73%</td>
<td>73%</td>
<td>73%</td>
<td>73%</td>
<td>73%</td>
<td></td>
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</tr>
<tr>
<td>Bear et al. [16]</td>
<td>2001</td>
<td>698</td>
<td>Neoadjuvant AT, adjuvant AT</td>
<td>2%, 78%, 65%, 78%</td>
<td>20%, 28%, 20%, 28%</td>
<td>12%, 28%, 20%, 28%</td>
<td>14%, 28%, 20%, 28%</td>
<td>2%</td>
<td>78%</td>
<td>65%, 78%</td>
<td>2%</td>
<td>78%</td>
<td>65%, 78%</td>
<td>2%</td>
<td>78%</td>
</tr>
</tbody>
</table>

**BR, response rate; DFS, disease-free survival; OS, overall survival; NR, not reported; N/A, not applicable; FAC, fluorouracil + doxorubicin + cyclophosphamide; AT, doxorubicin + paclitaxel; 2M, mitoxantrone + methotrexate with tamoxifen; 3M, mitoxantrone + fluorouracil + vincristine; CMF, cyclophosphamide + methotrexate + fluorouracil; 12M, fluorouracil + epirubicin + cyclophosphamide + mitomycin C + vincristine followed by mitomycin C + fluorouracil + vindesine.**
PREDICTORS OF RESPONSE AND MANAGEMENT OF NON-RESPONDERS TO NEOADJUVANT CHEMOTHERAPY

Despite the compelling preclinical data and theoretical advantages, survival benefit to neoadjuvant chemotherapy has not been convincingly demonstrated in clinical trials. Neoadjuvant therapy does permit assessment of response to therapy, which does lend prognostic information. Many patients who have a complete clinical response will have pathologic evidence of residual tumor, and occasionally patients with a clinical partial response will have no viable tumor in the surgical specimen. In most cases, lack of a clinical response to chemotherapy is a negative predictive factor for achieving pathologic complete response (pCR) [25].

The tumor profile has been identified as a predictor of clinical and pathologic response to neoadjuvant therapy. Bonadonna et al. [18] observed a higher overall response rate in patients with ER-negative versus ER-positive tumors and with PR-negative versus PR-positive tumors. A large study by Kuerer et al. [26] demonstrated that ER-negative status and higher nuclear grade were independently associated with pCR. The Southwest Oncology Group (SWOG)-0012 trial comparing classical neoadjuvant chemotherapy with metronomic chemotherapy demonstrated lower pCR rates in patients with either ER- or PR- tumors than those with ER+ or PR+ tumors [27].

Patients who do not achieve a clinical response from neoadjuvant therapy have a poor outcome. One of the proposed advantages of neoadjuvant chemotherapy was to identify non-responders to systemic chemotherapy. This in vivo model of chemosensitivity would theoretically allow a different, non-cross resistant chemotherapy regimen to replace the ineffective regimen. Unfortunately, attempts to exploit this in vivo model have met with disappointing results. In a study by the Aberdeen group, patients with large or locally advanced breast cancer received neoadjuvant cyclophosphamide, vincristine, doxorubicin, and prednisone (CVAP) [28]. Of the 159 patients, 104 demonstrated a clinical response. These patients were then randomly assigned to continue CVAP or to receive docetaxel (T), a non-cross resistant agent. The non-responders all received T. Switching to T resulted in a pCR rate of 34% in responders and 2% in non-responders.

The second part of the GeparTriO trial randomized patients who were non-responsive to neoadjuvant TAC to continue with TAC or to switch to vinorelbine and capecitabine [29]. Over 300 patients were included in each study arm, and the pCR rate was about 5% in both groups. These disappointing results suggested that non-responders have chemoresistant disease, and changing to a different regimen appears to not be of much utility.

For patients who do not achieve a pCR after neoadjuvant therapy, further chemotherapy after surgical resection does not appear to be of much benefit. In a study by Thomas et al. [30], 193 patients with locally advanced breast cancer received neoadjuvant CAVP and had a clinical response rate of 83.4% and a pCR rate of 12.2%. Of the 106 patients who did not achieve pCR, 51 were randomized to receive additional CAVP and 55 received vinblastine, methotrexate, leucovorin, and fluorouracil (VBMF). Disease-free and overall survival rates were not statistically different between the two groups, suggesting little benefit to postoperative (adjuvant) chemotherapy when neoadjuvant therapy does not induce a pCR. Outside of a clinical trial, patients who complete standard neoadjuvant therapy should not be given additional chemotherapy after surgery, even if pCR is not achieved.

NEOADJUVANT TARGETED THERAPY

Amplification of the HER2/neu gene in breast cancer is a poor prognostic feature, associated with advanced stage and higher grade. The HER2/neu protein, an epidermal growth factor (EGF) receptor, has been successfully targeted by the development of monoclonal antibodies, such as trastuzumab. Use of these antibodies has impressively affected the natural history of HER2+ tumors, and their incorporation into adjuvant and metastatic treatment programs has become standard practice. Their use has now been studied in patients who are candidates for neoadjuvant therapy, with equal success.

In a study by Buzdar et al. [31], 64 patients with HER2+ inoperable breast cancer were randomized to receive neoadjuvant paclitaxel followed by fluorouracil + epirubicin + cyclophosphamide (FEC). Of these, 19 were randomized to FEC alone while 23 were randomized to FEC with 24 weeks of trastuzumab (22 were later added and assigned to receive trastuzumab). The pCR rate was 60% in those receiving trastuzumab and was 26% for patients who did not receive trastuzumab. Neoadjuvant docetaxel and carboplatin (TC) was compared to the same combination with trastuzumab (TCH) in a phase II study published in abstract form by Chang et al. [32]. The pCR rate was 36% for the 11 patients receiving trastuzumab and was 9% for the 11 patients not receiving trastuzumab, with comparable cardiotoxicity rates.

Lapatinib is a tyrosine kinase inhibitor, which targets both the HER2 receptor and the EGF receptor. This agent is the focus of several planned trials including Neo-ALTO, a phase III randomized trial administering neoadjuvant paclitaxel with lapatinib, trastuzumab, or both agents together [33]. The NSABP B-41 trial will also examine lapatinib in a phase III study in which patients receive neoadjuvant AC and are then randomized to receive either lapatinib, trastuzumab, or both agents [34].

NEOADJUVANT ENDOCRINE THERAPY

Though there is a large body of evidence for neoadjuvant chemotherapy, preoperative endocrine therapy has been shown to be safe and effective for patients with ER+ tumors. Responses have been moderate, with pCRs relatively uncommon. Neoadjuvant endocrine therapy was initially limited to elderly patients who were not felt to be good candidates for systemic chemotherapy, due to either co-morbidities or to limited lifespan. The somewhat lower response rates were often an acceptable exchange for decreased morbidity associated with treatment. Several early trials comparing neoadjuvant tamoxifen followed by surgical resection to resection followed by adjuvant tamoxifen demonstrated no significant differences in overall survival rates [35–37]. In a study of patients >70 years of age with locally advanced breast cancer, Horobin et al. [38] identified clinical responses rates to neoadjuvant tamoxifen which were complete in 33%, partial in 15%, and unchanged in 30%. These data established neoadjuvant tamoxifen as a reasonable option for older patients.

As the efficacy of aromatase inhibitors (AI) in the adjuvant setting was established, several studies compared AI to tamoxifen in the neoadjuvant setting. After early favorable trials comparing neoadjuvant tamoxifen with anastrozole, tamoxifen and an AI were studied in the IMPACT trial, in which postmenopausal patients with ER+ tumors were randomized to receive 3 months of neoadjuvant anastrozole, tamoxifen, or the two together [39]. Results from this double-blinded, randomized trial demonstrated no differences in clinical response rates between groups (about 37%), with BCT rates of 44%, 31%, and 24%, respectively.

In a phase II study comparing neoadjuvant endocrine therapy to neoadjuvant chemotherapy, 239 postmenopausal patients with ER+ tumors were randomized to endocrine therapy (second randomization to either exemestane or anastrazole for 3 months) or chemotherapy (doxorubicin and paclitaxel every 3 weeks for four cycles) prior to surgical resection [40]. There were no differences between the two groups in rates of clinical response, pCR, or BCT.
NEOADJUVANT CHEMOTHERAPY: IMPLICATIONS FOR BCT

Factors that have been shown to affect local recurrence rates after neoadjuvant therapy and subsequent BCT are initial tumor size, presence of lymphatic invasion, nodal status, or presence of diffuse microcalcinifications on mammogram [41,42]. The typical conundrum presented to the surgeon after neoadjuvant chemotherapy is that tumors do not shrink in a concentric fashion, rather they often shrink to “Swiss cheese” or multicentric smaller deposits of tumor. How to best assess clinical response to neoadjuvant therapy is controversial, and physical exam is often unreliable. Many clinicians use mammography and/or ultrasound to determine tumor shrinkage, but breast MRI is an emerging yet controversial technique.

UTILITY OF MRI TO ASSESS RESPONSE TO NEOADJUVANT TREATMENT

MRI may be superior to physical examination, sonography, and mammography in assessing tumor response following neoadjuvant chemotherapy [43,44]. Therefore, MRI may become the ideal imaging modality in determining appropriate candidates for breast conservation after neoadjuvant chemotherapy. Several studies have demonstrated that MRI findings accurately predicted residual tumor size and correlated with pathological findings after resection [45–47]. However, the MRI findings may be influenced by the chemotherapy agents employed and the tumor phenotype. In a study of 55 patients who had neoadjuvant chemotherapy and MRI evaluation at various times through the course of neoadjuvant therapy, Chen et al. [45] found that a prediction of pCR by MRI criteria was accurate in 74% of patients and was influenced by the HER2 status of the tumor. The accuracy to predict a pCR by MRI was 50% for HER2-negative tumors versus 95% for HER2-positive tumors. In one of the largest studies of breast MRI and neoadjuvant chemotherapy, Chen et al. [48] showed that the presence of pCR or minimal residual disease prompted surgeons to recommend breast conservation surgery. The authors hypothesized that if MRI can accurately predict disease response, it could be a valuable tool for surgeons to aid them in recommending the appropriate surgical procedure. In an ancillary study, the same investigators demonstrated that the diagnostic performance of MRI was comparable between those patients receiving bevacizumab and those not receiving bevacizumab, with a significant limitation of MRI in cases in which tumor was “broken down” to scattered islands of tumor instead of shrinking in concentric fashion. MRI accurately predicted a pCR in 57% of the patients, with an overall diagnostic accuracy of 70% [49].

More studies are needed to evaluate the accuracy of breast MRI in patients undergoing neoadjuvant therapy, but it appears likely that MRI will have a role in the future management of these patients.

TIMING OF SENTINEL LYMPH NODE BIOPSY

The timing of sentinel lymph node biopsy in relation to neoadjuvant chemotherapy remains controversial. The status of the axillary lymph nodes is one of the most critical prognostic indicators for patients with invasive breast cancer, and yet axillary lymph node dissection remains one of the most morbid aspects of breast surgery [50]. Two of the initial goals of neoadjuvant therapy were to prevent excessive axillary surgery and to allow for BCT. Proponents in favor of sentinel node biopsy prior to neoadjuvant chemotherapy have argued that knowledge of the nodal status prior to treatment can influence choice of chemotherapy agents or radiation fields, while providing clinicians with an accurately staged patient. They also have argued that sentinel node biopsy after chemotherapy may not be accurate and may be associated with a high false-negative rate. There has been concern voiced by some investigators that neoadjuvant chemotherapy may alter the anatomy of the lymphatics, rendering the sentinel lymph node biopsy an inadequate representation of disease in the axilla after neoadjuvant treatment [51]. This concern was initially amplified by studies demonstrating low sentinel node identification rates and high false-negative rates [52–55]. These findings may have been attributed to the inclusion of patients in these studies with inflammatory tumors and clinically positive axillary lymph node metastases. Subsequently, studies of patients with clinically negative axillary lymph node status have demonstrated more favorable results with sentinel lymph node biopsy after neoadjuvant chemotherapy [56–59]. Multiple studies have now demonstrated that sentinel lymph node biopsy is feasible after neoadjuvant therapy, with acceptable sentinel lymph node identification rates and false-negative rates [60,61]. Without neoadjuvant chemotherapy, sentinel lymph node identification rates for patients with operable breast cancer have ranged from 84% to 100% with false-negative rates of 0–13% [62,63]. A recent meta-analysis was performed of literature between 1996 and 2007, including sentinel node mapping in patients with early-stage breast cancer after neoadjuvant chemotherapy [64]. The proportion of patients who had successful lymph node mapping ranged from 63% to 100%, with 79% of studies reporting a rate less than 95%. The summary rate of successful sentinel node identification was 89.6% (95% confidence interval [CI]: 0.860–0.923). The summary false-negative rate was 8.4% (95% CI: 0.064–0.109).

Proponents in favor of sentinel node biopsy after neoadjuvant chemotherapy have argued that this approach may spare approximately 20–30% of patients an axillary node dissection and its associated morbidity. In NSABP B-18, there was a significantly lower percentage of involved lymph nodes in the neoadjuvant chemotherapy arm versus the adjuvant chemotherapy arm (41% vs. 57%, P < 0.001) [22]. In NSABP B-27, where patients underwent sentinel node biopsy after neoadjuvant chemotherapy, 36% had a positive sentinel lymph node [23]. Sabel et al. [65] demonstrated that 50% of patients were sentinel node positive prior to neoadjuvant treatment. Thus, it appears that there will likely be more axillary dissections performed in patients having sentinel node biopsy prior to than subsequent to neoadjuvant chemotherapy.

REFERENCES

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