

Commentary

Clinical trial update: implications and management of residual disease after neoadjuvant therapy for breast cancerErica L Mayer¹, Lisa A Carey² and Harold J Burstein¹¹Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, USA²Lineberger Cancer Center, University of North Carolina, Chapel Hill, Chapel Hill, NC 27599, USACorresponding author: Erica L Mayer, emayer@partners.org

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Breast Cancer Research 2007, **9**:110 (doi:10.1186/bcr1755)**Abstract**

Neoadjuvant chemotherapy for breast cancer has a well-established role in the management of patients with locally advanced or early stage disease. Multiple trials have demonstrated superior survival outcomes in individuals achieving a pathologic complete response at the time of definitive surgery, and sophisticated genetic methods may predict which patients will be in this category. Those with less than a pathologic complete response remain at significant risk of recurrent disease, and currently no further standard therapy exists. Ongoing studies of novel agents may lead to improved therapeutic outcomes for this high-risk population.

Neoadjuvant or preoperative chemotherapy for operable breast cancer treatment was developed to achieve the goals of cytoreduction, with subsequent improvement in the ability to perform breast conservation, treatment of occult micro-metastatic disease, and assessment of *in vivo* sensitivity to a treatment regimen [1]. Multiple trials have demonstrated the benefits and role of treatment with neoadjuvant; however, few studies have evaluated the management of patients after the completion of neoadjuvant therapy, especially those with a suboptimal response.

Several large clinical trials have evaluated the role of neoadjuvant chemotherapy for breast cancer. National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 randomized 1,523 patients with operable breast cancer to receive four cycles of adriamycin and cyclophosphamide (AC) either before or after definitive surgery. In the group treated with neoadjuvant, a rate of pathologic complete response (pCR) in the breast of 13% was observed, with a significantly higher rate of breast conservation (67% versus 60%; $P=0.002$) At a median follow-up of 9 years, comparison between the groups treated with neoadjuvant and with

adjuvant demonstrated no differences in either disease-free survival (DFS) or overall survival (OS). However, when segregated by pathologic response to treatment with neoadjuvant, individuals achieving a pCR experienced significantly improved outcomes compared with non-pCR subjects, including 9-year DFS (75% versus 58%) and OS (85% versus 73%), and a 50% decrease in the risk of death compared with all other pathologic outcomes (relative risk 0.50, 95% confidence interval 0.32 to 0.78) [2,3]. In a similar study, the European Organization for Research and Treatment of Cancer (EORTC) randomized 698 subjects to anthracycline-based chemotherapy before or after surgery. Again, despite there being no differences in DFS or OS between the neoadjuvant and adjuvant groups, the pCR subgroup, defined as no residual invasive tumor in breast or lymph node tissue, did show improved OS (hazard ratio (HR) 0.86, 95% confidence interval 0.77 to 0.96, $P=0.008$) [4]. To investigate the role of exposure to neoadjuvant taxane, the NSABP randomized 2,411 subjects in study B-27 to neoadjuvant AC alone, to neoadjuvant AC and docetaxel before surgery, or to neoadjuvant AC with adjuvant docetaxel after surgery. The addition of the preoperative taxane led to an increased rate of pCR (26% with docetaxel versus 14% without docetaxel, $P<0.001$); because pCR was defined in the breast tissue only, removing the 15% of patients categorized as pCR with continued lymph node involvement leads to true pCR rates of 21.8% with docetaxel versus 11.5% without docetaxel [5]. At a median follow-up of 6.5 years, individuals achieving pCR demonstrated significantly improved survival compared with those without pCR (DFS HR 0.45, $P<0.001$; OS HR 0.33, $P<0.0001$) [6].

Efforts have been made to identify more accurately patients who are more likely to achieve pCR with neoadjuvant chemo-

AC = adriamycin and cyclophosphamide; DFS = disease-free survival; HR = hazard ratio; NX = vinorelbine and capecitabine; OS = overall survival; pCR = pathologic complete response; RCB = residual cancer burden; TAC = docetaxel, doxorubicin, cyclophosphamide; VACP = vincristine, doxorubicin, cyclophosphamide, and prednisone; VbMP = vinblastine, methotrexate, and prednisone.

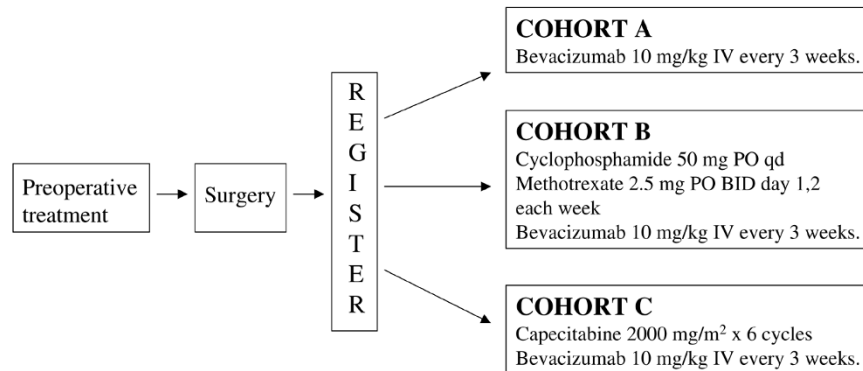
therapy. Historical experience suggests that hormone-receptor negative tumors are far more likely to achieve pCR than hormone-receptor positive tumors (20% versus 5% in a retrospective analysis) [7], and similarly ductal carcinomas may often achieve pCR whereas lobular carcinomas rarely do (less than 3% in larger experiences with up to 100 patients). A recently reported nomogram uses clinical and pathologic variables to predict likelihood of pCR in the breast and axilla with neoadjuvant anthracycline-based treatment. This nomogram includes independent predictors such as clinical stage at diagnosis, hormone receptor status, histologic grade, and number of preoperative chemotherapy cycles, and is able to predict pCR with reasonable accuracy [8].

Molecular assays have also been used to predict the likelihood of pCR in patients receiving neoadjuvant chemotherapy. The 21-gene recurrence score assay, which quantifies the levels of expression of 16 genes involved in breast cancer pathogenesis, has been shown to predict whether patients are likely to achieve pCR in response to anthracycline- and taxane-based chemotherapy [9]. Tumors with low recurrence scores, which tend to have higher levels of hormone receptor expression, lower levels of HER2 expression, and lower grade, are far less likely to reach pCR than tumors with higher recurrence scores. Gene expression arrays can also classify tumor specimens into several subgroups, including the hormone-receptor positive luminal subtypes A and B, as well as the HER2⁺/ER⁻ (where ER is estrogen receptor) subtype and the basal-like subtype, which typically underexpresses both hormone receptors and Her2; variable prognoses are observed for different subtypes [10-12]. Microarray analysis of preoperative samples before neoadjuvant anthracycline-based chemotherapy has demonstrated significant differences in the rates of pCR among the four molecular subtypes, with the highest rates of pCR seen in the basal-like and HER2⁺ subgroups (45%) and lower rates for the luminal tumors (6%) [13]. Among the hormone-receptor negative patients who fail to achieve pCR, there is a particularly high rate of early recurrence [14].

Although a lack of pCR portends a worse outcome, developing evidence suggests that there may be heterogeneity in outcome within the non-pCR group. Residual cancer burden (RCB), an index calculated from measurements of residual disease size and cellularity in the primary tumor and nodal metastases, has been evaluated in patients participating in two studies of neoadjuvant chemotherapy at the MD Anderson Cancer Center. Using a three-tier grading system, RCB was found to be a continuous predictor of DFS, with the patients at highest risk having the highest category of RCB [15]. Furthermore, expression array analysis of samples from NSABP B-27 demonstrates segregation of the non-pCR group into low-risk and high-risk categories, with differential survival outcomes [16]. Future use of these novel prognostic tools may better discriminate which patients with residual disease should receive further

treatment from those with a favorable enough prognosis to defer further therapy.

Currently, for most patients who do not achieve pCR after treatment with a well-studied neoadjuvant chemotherapy regimen [17], there is no evidence to support the use of further adjuvant chemotherapy. The only exception would be a patient who received only a portion of the chemotherapy regimen (for example a patient who received four cycles of AC and could go on to receive four additional cycles of a taxane). For the patient who has received a complete course of chemotherapy, any additional chemotherapy should be offered in the context of a clinical trial. Patients with hormone-receptor positive or Her2-positive disease certainly should receive appropriate adjuvant endocrine or trastuzumab therapy. Considering that residual disease may reflect resistance to the neoadjuvant chemotherapy, pilot trials have attempted to offer further non-cross-resistant chemotherapy in the adjuvant setting. In a trial from the MD Anderson Cancer Center, 110 patients who had received neoadjuvant VACP (vincristine, doxorubicin, cyclophosphamide, and prednisone) without pCR were randomized to further treatment with VACP or VbMP (vinblastine, methotrexate, and prednisone). Results demonstrated that further treatment with adjuvant was tolerable, with the suggestion of improved outcomes in the VbMP arm over the VACP arm (OS 65% versus 47%, $P=0.06$) [18]. In the small ICARO 1 study, presented in abstract form at the 2006 San Antonio Breast Cancer Symposium, 48 patients with clinical T4 disease were treated with neoadjuvant PEV (cisplatin, epirubicin, and vinorelbine), surgery, radiation, adjuvant CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) for six cycles, and endocrine therapy if indicated. Individuals who did not achieve pCR at the time of surgery ($n=35$) were randomized to observation ($n=28$) or reinduction therapy with epirubicin and sequential docetaxel ($n=7$). At a median follow-up of 72 months, DFS and OS were significantly better in the reinduction group than in the observation group (100% versus 53%, $P=0.009$; 100% versus 68%, $P=0.05$, respectively) [19]. Although provocative, the numbers in this trial are too small for any definitive conclusions to be drawn. However, both studies suggest that further non-cross-reactive treatment may be of value. The GeparTrio study examined the effect of providing a non-cross-reactive regimen (NX; vinorelbine and capecitabine) to individuals without evidence of clinical response after two cycles of preoperative TAC (docetaxel, doxorubicin, cyclophosphamide). In the 74 patients studied, pCR rates were not significantly improved with the non-cross-reactive NX regimen compared with those receiving further TAC (3.1% versus 7.3%) [20]. Despite the apparent lack of benefit from the non-cross-reactive regimen in this setting, the role of a novel regimen for non-responders completing an entire, rather than an abbreviated, course of preoperative treatment is unknown, as are long-term effects on outcome.

Figure 1

Schema for multicenter pilot study of angiogenesis inhibitor therapy after neoadjuvant chemotherapy. BID, twice a day; IV, intravenously; PO, orally; qd, once daily.

An alternative mechanism for targeting chemotherapy-resistant disease may be through novel treatment approaches, such as the use of angiogenesis inhibitors. The primary agent in this class, bevacizumab, has already demonstrated marked benefits in several types of solid tumor [21,22]. In metastatic breast cancer, initial examination of bevacizumab with capecitabine chemotherapy in pretreated disease showed an improved response rate that did not translate into improved DFS or OS [23]. Subsequently, the addition of bevacizumab to paclitaxel chemotherapy in the first-line setting showed improvements in both response and DFS [24]. Another tool in targeting angiogenesis, metronomic chemotherapy (continuous low-dose oral treatment with cyclophosphamide and methotrexate) has also demonstrated activity in the metastatic setting in combination with bevacizumab [25]. It is possible that other novel biological therapies that show promise in breast cancer treatment may also have a role in the post-preoperative setting.

An ongoing multicenter pilot trial, led by investigators at the Dana-Farber Cancer Institute, is evaluating the feasibility and toxicity of 1 year of angiogenesis inhibitor therapy for individuals with less than a pCR after neoadjuvant chemotherapy (see Figure 1). Eligibility includes residual invasive disease in the breast or lymph node tissue after treatment with neoadjuvant, and receipt of a standard chemotherapy regimen, either preoperatively or postoperatively. In the first of three cohorts, 40 women have been treated with 1 year of adjuvant bevacizumab. This cohort included 45% women with stage III disease at diagnosis and 58% who were hormone-receptor positive. Therapy was generally well tolerated, with treatment-related toxicities including mild arthralgias (50%), headache (50%), epistaxis (20%), and hypertension (23%). Significant toxicities included one case of reversible posterior leukoencephalopathy and one patient with gastrointestinal bleeding. With a median follow-up of 8 months, four patients have recurred, underscoring the high-

risk nature of this population. Extended follow-up from this study will evaluate possible long-term cardiovascular side effects from prolonged bevacizumab exposure. Accrual continues in the two other cohorts, which offer 1 year of bevacizumab paired with oral chemotherapy, either 6 months of metronomic chemotherapy or six cycles of capecitabine. Data from this pilot study will be used to design a phase III trial for this patient population randomizing to one of three arms: 1 year of bevacizumab, six cycles of capecitabine, or a combination of the two [26].

Conclusion

Neoadjuvant chemotherapy is an evolving strategy for treating locally advanced and early stage breast cancer. One potential advantage of treatment with neoadjuvant therapy is the opportunity to use pathologic response at the time of surgery to stratify patients by risk and subsequently select those for whom further therapeutic recommendations may be beneficial. As yet, the use of such dynamic tumor response information to guide clinical recommendations is in the investigative stages. However, it is hoped that the design of future clinical trials will allow an objective assessment of this management approach.

Competing interests

EM receives research funding from Genentech; LC is on the Advisory Boards and Speakers' Bureau of Genentech and receives research funding from Genentech; HB is on the Speakers' Bureau of Genentech and receives research funding from Genentech.

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