Milestone clinical trials of the National Surgical Adjuvant Breast and Bowel Project (NSABP)

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Abstract: The National Surgical Adjuvant Breast and Bowel Project (NSABP) has made significant contributions in reducing the extent of breast surgery and in improving outcomes of patients with early-stage breast cancer through the conduct of large randomized clinical trials evaluating local and systemic therapy. In 2014, the NSABP merged with two other US National Cancer Institute-funded cooperative groups, the Radiation Therapy Oncology Group (RTOG) and the Gynecologic Oncology Group (GOG), to form NRG Oncology. The combined organization has 218 member institutions with more than 600 affiliate centers located throughout the United States, Canada, Puerto Rico, and other international sites. Over the past half century, the NSABP has entered more than 150,000 women into clinical trials of breast cancer treatment and breast cancer prevention. Many of these trials have been instrumental in establishing new standards of care for patients with breast cancer.

Keywords: Breast cancer; clinical trials; systemic therapy for breast cancer; locoregional therapy for breast cancer

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Background

On April 4, 1958, the first patient was enrolled in the first randomized clinical trial conducted by an organization that was to become the National Surgical Adjuvant Breast and Bowel Project (NSABP). Now, close to 60 years later, the treatment of breast and bowel cancer has changed dramatically in large part because of the trials conducted by the NSABP. These trials have had a profound impact on our understanding and treatment of these diseases.

Today there are 218 member institutions with more than 600 affiliate centers located throughout the United States, Canada, Puerto Rico, and other international sites. In 2014, the NSABP merged with two other US NCI-funded cooperative groups, the Radiation Therapy Oncology Group (RTOG) and the Gynecologic Oncology Group (GOG), to form NRG Oncology. Many of the member institutions are university hospitals or large comprehensive cancer centers, but the majority of these sites are community-based institutions. This allows patients the opportunity to enter studies without the burden or cost of travel to academic centers.

The initial studies of the NSABP focused on the effectiveness of thiotepa, 5-FU (fluorouracil), radiotherapy, or oophorectomy in the adjuvant treatment of patients with breast cancer following radical mastectomy (1). The group's studies today continue to focus on the locoregional and adjuvant therapy of both breast and colorectal cancer, with the goal of improving the survival and the quality of life of

patients with these diseases. This report will focus on the landmark breast clinical trials.

Breast cancer trials

Locoregional treatment studies

NSABP studies have evaluated locoregional therapies for breast cancer, and results from these trials have been instrumental in changing the surgical management of both invasive and non-invasive breast cancer.

One of the NSABP's first studies, Protocol B-04, addressed the question of whether total mastectomy with or without radiotherapy in patients with operable breast cancer would result in outcomes similar to those achieved with radical mastectomy. The initial results were published in 1977. With a total of 1,765 women enrolled, B-04 demonstrated no significant difference in disease-free survival (DFS) or overall survival (OS) among the various treatment groups (2). After 25 years of follow-up, the results continue to demonstrate no significant differences in long-term outcomes between the clinically node-negative patients who underwent radical mastectomy and those who underwent total mastectomy with or without radiotherapy or between the clinically node-positive patients who underwent radical mastectomy and those who underwent total mastectomy with radiotherapy (3).

The results of the B-04 trial had a profound impact on the surgical management of breast cancer and led to the conduct of NSABP Protocol B-06. In this trial, 2,163 patients with invasive breast cancers ≤4 cm were randomly assigned to receive either a modified radical mastectomy, or lumpectomy, or lumpectomy with breast radiotherapy. After 20 years of follow-up, there continue to be no significant differences in OS, DFS, or distant disease-free survival (DDFS) among the three groups of patients (4,5).

NSABP Protocol B-32 addressed the question of whether sentinel lymph node (SLN) resection in patients with clinically node-negative breast cancer would result in similar outcomes as SLN resection followed by axillary lymph node dissection (ALND). A total 5,611 women were randomly assigned to SLN resection plus ALND or to SLN resection alone with ALND only if the SLNs were positive. This study demonstrated no significant differences in DFS, OS, or locoregional control among the two groups (6) but showed significantly less arm morbidity with SLN resection alone.

Despite the increasing use of lumpectomy for the treatment of invasive disease in the 1990s, ductal carcinoma *in situ* (DCIS) was still routinely treated with mastectomy. The NSABP was among the first groups to evaluate breast conservation in patients with DCIS. Protocol B-17 compared lumpectomy alone to lumpectomy plus breast radiotherapy in patients with localized DCIS and demonstrated after 12 years of follow-up that radiotherapy significantly reduced the rate of both invasive and non-invasive ipsilateral breast tumor recurrence (7). Subsequent NSABP trials in patients with DCIS who underwent lumpectomy plus breast radiotherapy evaluated the role of tamoxifen, anastrozole, and trastuzumab.

Ongoing NSABP studies are continuing to explore new therapies designed to improve the locoregional management of breast cancer.

Adjuvant therapy trials for breast cancer

An extensive series of adjuvant therapy trials have been conducted to evaluate systemic treatments in patients with node-negative or node-positive disease.

Between 1972 and 1974, 380 women with node-positive breast cancer were randomly assigned to receive either L-phenylalanine mustard (L-PAM) or placebo following primary breast cancer surgery in the NSABP B-05 trial. Results documented that postoperative adjuvant therapy could impact the natural history of breast cancer and reduce the risk of recurrence (8). Subsequent trials in patients with node-positive disease have studied combination chemotherapy, incorporating anthracyclines (doxorubicin/cyclophosphamide, AC) and sequential or combination chemotherapy with anthracyclines and taxanes (AC→T, TAC, dose-dense AC→T).

Protocol B-09 compared combination chemotherapy with and without tamoxifen and also included a quality assurance program for estrogen receptor analysis. The results of this study demonstrated that the addition of tamoxifen to chemotherapy improved outcomes in node-positive, receptor-positive patients (9).

Selective aromatase inhibitors (AI's) are widely utilized for postmenopausal women with hormone-receptor-positive breast cancer. NSABP Protocol B-42 will determine if prolonged adjuvant hormonal therapy with letrozole improves DFS in postmenopausal women with ER-positive and/or PgR-positive tumors who have completed 5 years of hormonal therapy with either 5 years of an AI or up to 3 years of tamoxifen followed by an AI. This study has completed accrual and will address the AI duration question.

NSABP Protocol B-31 evaluated the use of trastuzumab (Herceptin®) plus adjuvant chemotherapy in node-positive patients with HER2-positive breast cancer. The results of this study were combined with those from NCCTG trial 9831 (10) and demonstrated a 40% relative reduction in DFS events and a 37% reduction in deaths with the addition of trastuzumab to adjuvant chemotherapy *vs.* adjuvant chemotherapy alone.

The NSABP has conducted adjuvant trials in node-negative breast cancer with the initiation of NSABP Protocol B-13, which evaluated chemotherapy in node-negative, ER-negative patients and B-14, which evaluated tamoxifen alone in node-negative, ER-positive patients. Both studies demonstrated improvement in outcomes in favor of the active treatment (11,12). Subsequent NSABP trials in patients with node-negative breast cancer have evaluated other combinations of therapy, including the combination of chemotherapy and tamoxifen.

The OlympiA trial [NSABP B-55/Breast International Group (BIG) 6-13] is a global indication study evaluating the effectiveness of olaparib in patients with a BRCA mutation and stage II or III breast cancer. Patients with triple negative or hormone-receptor-positive/HER2-negative breast cancer are randomly assigned to olaparib or placebo after completing standard therapy with neoadjuvant or adjuvant chemotherapy, surgery, and radiation if indicated. This study is currently accruing with a goal of enrolling 1,500 patients. There are unique aspects of this trial structure, which may serve as the model for future trials. The study is a collaboration between two global academic groups, BIG, sponsored by Astra-Zeneca, and NRG Oncology, sponsored by the NCI. There is a single protocol with two versions that differ only in logistical content. The analysis will be consolidated in a single combined database.

Neoadjuvant therapy trials for breast cancer

In 1988, the first NSABP neoadjuvant trial (B-18) evaluated four cycles of AC administered either postoperatively or preoperatively. A pathological complete response (pCR) was documented in 13% of patients. Administration of preoperative AC resulted in a statistically significant increase in incidence of pathologic negative axillary lymph nodes compared with patients randomly assigned to postoperative AC (58% *vs.* 42%, P<0.0001). The preoperative group was also more likely to undergo breast-conserving surgery compared to the postoperative group (68% *vs.* 60%, P=0.001) but there were no statistically significant differences in DFS or OS between the two groups (13). NSABP B-27 was designed to determine the effect of adding docetaxel to preoperative AC. The addition of preoperative docetaxel to AC increased pCR rates compared to preoperative AC alone (26% *vs.* 13%, P<0.0001) but it did not statistically significantly improve DFS or OS (13). In both studies, patients who achieve a pCR have improved outcomes.

The U.S. Food and Drug Administration had established an international working group known as the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) to collaborate on a pooled analysis of neoadjuvant trials with long-term data (14). NSABP B-18 and NSABP B-27 were included in the pooled analysis. Data were obtained from 12 international trials with 11,955 patients. The association was strongest between pathologic response and long-term outcomes in patients with triple-negative breast cancer [event-free survival (EFS): HR 0.24, 95% CI, 0.18–0.33; OS: 0.16, 0.11–0.25] and in those with HER2-positive, hormone-receptor-negative tumors who received trastuzumab (EFS: 0.15, 0.09–0.27; OS: 0.08, 0.03–0.22).

These data supported the opening of an accelerated drug approval pathway by the US FDA for patients with high-risk early-stage breast cancer.

Effect of endocrine therapy in DCIS

NSABP Protocol B-24 (15), begun in 1991, evaluated tamoxifen in patients with DCIS treated by lumpectomy and breast radiotherapy. Tamoxifen statistically significantly reduced the risk of invasive breast cancer events, although the benefit was largely restricted to patients with ER-positive DCIS. There were 43% fewer invasive breast cancer events in the tamoxifen group (rate ratio 0.57; 95% CI, 0.38–0.85; P=0.004). Protocol B-35 (16) is a phase III trial that randomly assigned 3,014 patients with ER-positive and/or PgR-positive DCIS treated with lumpectomy and radiotherapy to tamoxifen *vs.* anastrozole for 5 years. Patients receiving anastrozole had a statistically significant improvement in breast cancer interval events compared to those receiving tamoxifen (HR 0.73; 95% CI, 0.56–0.96; P=0.023). This trial showed that women can benefit from having a choice of effective agents for the adjuvant treatment of DCIS.

Chemoprevention trials

The NSABP also completed two large breast cancer

chemoprevention studies, the Breast Cancer Prevention Trial (P-1/BCPT) (17), and the Study of Tamoxifen and Raloxifene (STAR) (18). These studies screened more than 1/4 million women and randomly assigned more than 33,000 healthy women at increased risk for the future development of breast cancer. Both studies focused on the use of selective estrogen receptor modulators (SERMs) to reduce the development of primary invasive breast cancers. In the BCPT, between 1992 and 1997, more than 13,000 women were randomly assigned to receive either tamoxifen 20 mg or placebo daily for 5 years. The results demonstrated a highly statistically significant 49% ($P<0.00001$) reduction in invasive breast cancer (17). However, tamoxifen also increased the risk of uterine malignancy, thromboembolic events, and cataracts. These events occurred more frequently in women ≥50 years old.

The STAR trial (18) began in 1999 and enrolled more than 19,000 women. These postmenopausal women were randomly assigned to either tamoxifen (20 mg daily) or raloxifene (60 mg daily), which is a SERM approved in the United States for the treatment and prevention of osteoporosis. Women taking raloxifene for fracture prevention had been noted to have had a decrease in receptor-positive breast cancers with no excess in endometrial cancers.

The results of the STAR trial documented that tamoxifen and raloxifene were equally effective in reducing the risk of invasive breast cancer (risk ratio, 1.02; 95% CI, 0.82–1.28). Although raloxifene was not as effective as tamoxifen in preventing non-invasive breast cancer, its use resulted in fewer endometrial cancers, fewer venous thromboembolic events, and no excess of cataracts, making it an attractive option for the chemoprevention of breast cancer in postmenopausal women at increased risk.

Tissue bank and correlative science efforts of the NSABP

NSABP tissue bank

The NSABP Tissue Bank arose from the group's quality assurance program for diagnostic pathology. Although the intended requirement was to collect H&E-stained slides for central confirmation of cancer diagnosis, many sites decided to send tumor tissue blocks as an alternative. This resulted in the unplanned procurement of blocks from 30–40% of the NSABP trial cohort before 1996. There was no government funding available for tissue banking effort until that time.

In 1996, a new initiative under the current leadership of the NSABP expanded the tissue bank and correlative science within the group. Currently, the tissue bank houses tumor tissue blocks from more than 70,000 cases of breast and colorectal cancer from patients who participated in NSABP trials. Microarrays of tissue from all of the key trials that have been conducted are available in the tissue bank.

Correlative science efforts

Over the past three decades great achievements have been made in the treatment of breast cancer through clinical trials, and the future holds the promise of moving beyond strictly empirical approaches to the idea of trials designed to address the treatment and prevention of cancer based on biomarkers and genetic makeup.

We believe that the current trial mechanism of including patients from different risk categories in a single trial should be examined to achieve a better selection process for patients participating in clinical trials. For example, we can employ banked materials from completed trials to develop context-specific prognostic markers that not only predict response to therapy but also provide an assessment of baseline risk of recurrence.

Along these lines, we have developed a context-specific marker for ER-positive, node-negative tamoxifen-treated patients to determine baseline risk that can be used in the decision of whether a patient should be offered chemotherapy. The OncotypeDX™ test, based on measurement of the mRNA expression levels in 21 genes (19) marks two significant paradigm shifts for correlative science studies: the test is a continuous predictor for individual risk of recurrence, and there is now recognition of the significance of the linearity of the assay. The OncotypeDX assay has set a benchmark for our current correlative science efforts. We have also developed a robust method for microarray gene expression profiling of formalin-fixed, paraffin-embedded tumor tissue blocks. This has virtually eliminated barriers to the interrogation of gene expression levels in archived materials in our tissue bank.

Conclusions

Over the past 60 years, randomized clinical trials conducted by the NSABP have resulted in dramatic improvements

in the treatment and prevention of breast cancer. These advances in our understanding of the biology of these diseases and in patient treatment and care would not have been possible without the willingness of the women and men who participate in these studies. We are grateful to the individuals who have entered NSABP trials over the past 60 years and to those participating in our current studies.

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Footnote

Conflicts of Interest: Dr. Mamounas—Consultant: Genomic Health, Genentech, Bayer, Pfizer, Biotheranostics, Celcuity, GRAIL, Macrogenics; Speakers' Bureau: Genomic Health, Genentech. All other authors have no conflicts of interest to declare.

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