Cancer and Leukemia Group B Breast Committee: Decades of Progress and Plans for the Future
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Abstract The Breast Committee of the Cancer and Leukemia Group B was formed in 1969 under the direction of James Holland. Initial studies examined combination chemotherapy for advanced disease. Although the committee has continued to conduct studies in patients with advanced disease, adjuvant therapy has been an even more important focus for the past 30 years. Over the past 20 years, studies have focused on optimization of chemotherapy through the testing of dose and schedule, the value of adding novel agents, and the role of biological agents. Current and future projects are aimed at exploiting and increasing our growing knowledge of the molecular biology of breast cancer by developing targeted therapies.

Breast cancer is a significant public health problem in the United States and virtually all industrialized societies. It is the most common life-threatening malignancy in American women and the second most frequent cause of cancer-related mortality. After peaking in 1990, the overall mortality for breast cancer has been declining in the United States despite a gradual increase in incidence (1).

In addition to effective screening and improved local therapy (surgery and radiation treatment), a key advance in the treatment of breast cancer is the availability of a range of systemic therapeutic options. Endocrine therapy, systemic chemotherapy, monoclonal antibodies, and antiangiogenic agents have all been shown to be effective in palliating symptoms and, in many cases, extending survival in advanced disease. Endocrine therapy, chemotherapy, and monoclonal antibody therapy with trastuzumab have also prevented or delayed relapse and death in early-stage disease.

The Cancer and Leukemia Group B (CALGB) Breast Committee has done a wide variety of clinical trials and has made a substantial contribution to our current understanding of breast cancer. Our committee has been instrumental in defining optimal chemotherapy regimens for women with stage I to IIIA breast cancer. We have also played a key role in showing that some very intensive and toxic treatments [e.g., high-dose chemotherapy with autologous or peripheral stem cell support, high-dose (>60 mg/m² per cycle) doxorubicin] are no better than less toxic approaches. In women with operable breast cancer, we have made seminal observations that have led to the current understanding of breast as a family of related diseases, not a single monolithic process. In patients with advanced disease, we have made equally important observations. We have defined the optimal dose and schedule of the paclitaxel, one of the most important agents in breast cancer treatment. We have also shown that the administration of investigational agents to women who have received limited prior treatment is an entirely safe approach. The Breast Committee has consistently designed trials that not only address a single question but also further our understanding of breast cancer by addressing a fundamental treatment principle. Since the mid-1980s, our trials have also addressed questions about the underlying biology of breast cancer and the interaction between the biological heterogeneity of breast cancer and treatment. We have only been able to include selected highlights in this article, but they were chosen to the steady progress in the use of systemic chemotherapy for all stages of the disease. Furthermore, these studies provide the foundation for the committee’s current focus on rational therapeutics based on molecular oncology advances.

Achievements of the Breast Committee

The accomplishments of the Breast Committee would not have been possible without the vision, intellect, and hard work of the chairs of the committee over the past three decades. As co-chairs of the present committee, we are fortunate to build on the work of Drs. Gerson Lesnick, William Wood, Craig Henderson, and Larry Norton with their vice-chairs Drs. Joseph Aisner, David Duggan, Daniel Hayes, and Hyman Muss. As we increasingly focus on molecularly driven research, we also want to recognize the ongoing contributions of Matthew Ellis, vice-chair for correlative science. Importantly, the prolific efforts, boundless energy, and intellectual might of the Breast Committee’s lead statistician Dr. Donald Berry has been critical to the progress described. Finally, we want to acknowledge the contributions of the other cooperative groups in North America that comprise The Breast Cancer Intergroup. The collaborative spirit of the Intergroup has contributed to the success of the CALGB Breast Committee and to progress in breast cancer research over the past 15 years.

Adjuvant chemotherapy is predicated on previously described models of cell growth and response to chemotherapy that suggest that earlier, rather than later, use of cytotoxic agents should be more effective, that full or optimal doses will be
superior to lower or suboptimal doses, and that the frequency of administration is an important variable. The Skipper-Shabel model and the Norton-Simon Hypothesis together provide support for these assertions, and the committee has endeavored to test the concepts prospectively (2, 3).

The use of empirical combinations of chemotherapy agents has a long tradition in medical oncology and has yielded impressive and curative advances in some disease. Yet, combinations can force dose reductions of the component agents to facilitate concurrent drug delivery. These reductions have the potential to compromise efficacy. Furthermore, the toxicity associated with combinations may prevent consistent treatment on a fixed schedule, potentially allowing for growth of otherwise sensitive tumor clones. To address these concerns, we have long studied sequential treatment plans. In these plans, we aim to deliver all of one treatment and then all of a second one. This sequential approach has several advantages over concurrent combinations and also over strictly alternating designs, including the ability to deliver the components at “optimal” rather than reduced doses. The second is the ability to maintain a more effective schedule without dose delays.

An early trial by the Breast Committee tested these concepts using CMFVP and VATH (C8082) as postoperative adjuvant therapy (4). Each regimen was considered state of the art and was active. The goal was to determine the value of stopping the cyclophosphamide/methotrexate/5-fluorouracil—type treatment and adding an anthracycline-based sequential (“cross-over”) regimen. Women randomized to receive the crossover regimen were less likely to develop recurrent disease in spite of the fact that the dose of doxorubicin, the most active agent in the crossover regimen, was substantially below currently accepted standard levels.

The Committee’s next major adjuvant trial (C8541) focused on identifying the optimal dose of anthracycline-based chemotherapy (5). The chemotherapy regimen tested included cyclophosphamide, doxorubicin, and 5-fluorouracil given every 4 weeks. Of note, the 5-fluorouracil was given on both days 1 and 8 of the 28-day cycle. Patients with involved lymph nodes were randomly assigned to one of three treatments: (a) low-dose cyclophosphamide/doxorubicin/5-fluorouracil (300, 30, 300 mg/m2) given once every 4 weeks for four cycles, (b) medium dose (400, 40, 400 mg/m2) for six cycles, or (c) high dose (600, 60, 600 mg/m2) for four cycles. The latter two arms had different dose intensity but in fact delivered the same total dosage of all three agents. The trial showed that the low dose was inferior to the other two and also suggested that the most dose-intensive arm (600, 60, 600 mg/m2) resulted in the best overall outcome. In a correlative science companion, it was shown that the dose-response relationship was most clearly seen among patients who had c-erbB-2/HER2–positive tumors as assessed by both immunohistochemistry and gene amplification (6). It was one of the first studies to suggest that molecular characterization of tumor cells could identify subgroups of patients who would have a greater or lesser benefit from adjuvant chemotherapy.

In the late-1980s, there was a growing interest in pursuing even more dose-intensive treatments in patients with breast cancer. In the metastatic setting, initial studies using high-dose chemotherapy plus autologous bone marrow support yielded very preliminary but promising results. The CALGB initiated a pilot study to test the feasibility of administering high-dose chemotherapy with bone marrow support to women with ≥10 positive axillary lymph nodes. The patient population was chosen based on the historically poor outcome for women with multi-node-positive breast cancer. Early results from the pilot study were promising, and the CALGB Breast Committee, working closely with the Transplant Committee, launched a large randomized trial (C9082) comparing high-dose chemotherapy with autologous bone marrow or peripheral stem cell support versus a less intensive treatment regimen (7). The use of high-dose chemotherapy with bone marrow support for women with breast cancer was one of the most controversial topics in medical oncology for a period of ~10 years. To a large extent, this controversy ended in May 1999 when the CALGB trial and two other randomized trials revealed no clear benefit in terms of either disease-free or overall survival as a result of the dose-intensified approach (8–10). The message from the study was clear: in spite of evidence that dose intensity is of importance in the treatment of breast cancer, there was no rationale to increase doses to the range that required bone marrow or peripheral stem cell support.

In the early to mid-1990s, the committee explored questions related to dose and schedule in both the metastatic and adjuvant settings. In the metastatic setting, C9342 tested the standard paclitaxel dose given as a 3-hour infusion against two higher dose levels (11). Women enrolled in this trial had received either one or no prior chemotherapy in the metastatic setting. The trial showed no advantage in terms of response rate, time to progression, or overall survival with the higher doses, and higher doses were clearly associated with greater toxicity. The 175 mg/m2 dose given every 3 weeks became the “gold standard” and was used widely in practice and in subsequent clinical trials, both in the metastatic and adjuvant settings.

Although C9342 was being conducted in the metastatic setting, the Committee also conducted C9344 in patients with node-positive breast cancer (12). Building on the results of C8541, C9344 compared three doses of doxorubicin (60, 75, and 90 mg/m2) given with a fixed dose of cyclophosphamide (600 mg/m2) every 3 weeks, for a total of four cycles. In addition, using a 3 × 2 factorial design, the study also randomized patients to receive either four cycles of paclitaxel (175 mg/m2 every 3 weeks) or no further therapy after the anthracycline-based regimen. Although the study showed no additional benefit with doxorubicin dose escalation, there was a clear improvement in disease-free and overall survival with the addition of the four cycles of paclitaxel. Indeed, this was the first trial to show an improvement in disease control in patients with early-stage disease as a result of a taxane. Furthermore, an important subtlety of this trial was that it randomly assigned patients to receive, or not, granulocyte colony-stimulating factor. This trial, hence, provides one of the first large and robust pieces of evidence for the lack of a direct oncologic effect for the growth factor and for its safety. This became important with C9741 discussed below.

Although the CALGB was conducting C9344, the National Surgical Adjuvant Breast and Bowel Project led two studies that evaluated the role of dose-intensive cyclophosphamide. These studies (National Surgical Adjuvant Breast and Bowel Project B-22 and B-25) showed no additional benefit with a 2- or 4-fold increase in the cyclophosphamide dose in women with node-positive breast cancer (13, 14). The two National Surgical Adjuvant Breast and Bowel Project studies and the three CALGB...
trials (C9082, C9342, and C9344) all indicated that escalating doses of chemotherapy to a supra-standard range resulted in greater toxicity without any added benefit. The strength of these studies lay in their size, the diversity of the patient population (metastatic, multi-node-positive stage II/III, and standard adjuvant), and the consistency of the finding (i.e., no additional benefit beyond standard doses) across three different chemotherapeutic agents. Taken together, these studies strongly suggest that there is a threshold effect for chemotherapy dose in women with breast. Although suboptimal doses of chemotherapy should be avoided, administering higher than standard doses is unlikely to result in additional benefit and will, almost certainly, result in greater toxicity.

In the next generation of trials, the Breast Committee opted to move beyond questions of dose intensity and, instead, focus on scheduling issues. In the adjuvant setting, CALGB 9741 used a factorial design to test two chemotherapy questions in patients with node-positive early-stage breast cancer (15). The study compared the sequential doxorubicin (A), paclitaxel (T), and cyclophosphamide (C) versus concurrent doxorubicin and cyclophosphamide (AC) followed by paclitaxel (T). In addition, C9741 looked the administration of chemotherapy cycles using a standard every 3-week schedule versus a dose-dense every 2-week schedule. Preclinical mathematical and laboratory modeling had suggested that the more frequent administration would reduce the risk of disease recurrence, and C9741 was designed to test that hypothesis. In addition, by comparing the concurrent versus sequential chemotherapy of chemotherapy, they challenged a widely held view among oncologists that combinations of agents are necessarily more active than sequential single agent therapy. The primary end points were disease-free and overall survival, and the secondary end point was toxicity. The initial analysis at a median follow-up of 36 months showed that dose-dense treatment improved the primary end points: disease-free survival (risk ratio, 0.74; \( P = 0.010 \)) and overall survival (risk ratio, 0.69; \( P = 0.013 \)). A recent update at 6.5 years median follow-up confirmed the stability of these results and showed no increase in long-term toxicities. The every 2-week schedule was particularly effective in the large subgroup of women with hormone receptor-negative breast. Furthermore, as above, the benefits of the dose-dense treatment could not be ascribed to the use of growth factor support (as discussed above with regard to C9344); thus, this trial provides important confirmation of the value of dose scheduling in the curative treatment of human malignancy. Finally, this study has established a new standard for patients with early-stage breast cancer. Although it is not the only chemotherapy regimen that is used in this setting, it is widely given and has formed the backbone of numerous successor trials.

C8541, C9344, and C9741 each showed an improvement in disease-free and overall survival as a result of treatment with one of the investigational arms (higher-dose cyclophosphamide/doxorubicin/fluorouracil in C8541, paclitaxel in C9344, and dose-dense therapy in C9741). In an effort to understand whether these improvements in outcome were distributed across all patients, we retrospectively analyzed the interaction between treatment arm and hormone receptor status in women who received adjuvant endocrine therapy (generally tamoxifen) (16). This exploratory analysis strongly suggests that in each of the trials, the “better” chemotherapy is most easily identified among patients with estrogen receptor (ER)–negative cancers. Women with ER-positive cancers seem to derive benefit from the “better” or more intensive treatment arms, but the degree of benefit is far less than in those with ER-negative tumors. Analysis of the annual hazard rate for recurrence links this observation to the underlying biology of breast cancer because it is the subset of patients with high early risk of recurrence (ER negatives) who gain early and significantly from the “better” chemotherapy that is presumably more effective in the treatment of rapidly growing tumors. In considering the combined analysis of the three trials, it is important to consider the lack of centralized testing for hormone receptors, and the fact that the use of endocrine therapy was not monitored over time. These issues form a core motivation for our prospectively defined correlative science studies now planned. One also has to be extremely careful in making comparisons across studies. However, the findings from this analysis are both striking and consistent with other data sets. The challenge, as we move forward, will be to identify which women with ER-positive disease derive the greatest benefit from chemotherapy. Other studies suggest that ER-positive breast cancer is quite heterogeneous, and that it will be a subset of tumors based on molecular phenotype that benefit (or not) even when the hormone receptors are expressed.

With each successive adjuvant trial, the absolute number of events we have observed has steadily declined. This reduction in recurrences and deaths may relate to an increase in the proportion of cases that are detected through screening and subtle shifts in the breast cancer patient population over time. We are fortunate to have long-term results from C7581, a trial that explored cyclophosphamide/methotrexate/5-fluorouracil-based chemotherapy in women with node-positive breast cancer (17). An update from this study described the 20-year natural history of the trial population. Although the benefits of chemotherapy seemed to be long lasting, the study emphasized the importance of long-term follow-up in women with breast cancer, as late recurrences and even later deaths secondary to breast cancer are not uncommon. As we move forward, this study is a reminder that we may need to separate and independent strategies to reduce the risk of early and late recurrence in women with breast cancer.

Finally, we have a long-standing interest in the treatment of breast cancer in older patient populations. We recognize the differences between the typical protocol patient with a median age in her late 40s and a patient with the median age of breast cancer in the general population (early 60s). To that end, we recently explored the role of radiation added to lumpectomy plus tamoxifen in women ages \( \geq 70 \) years with clinical stage I, ER-positive breast cancer (18). This trial (C9343) showed a very low rate of death from breast cancer and a very low rate of in-breast recurrences. It clearly suggests that radiation therapy may not be necessary for all patients over age 70. Presently, our focus on older patients in the adjuvant setting led us to design the only U.S. trial testing adjuvant chemotherapy specifically in this age group. We are comparing single-agent capcitabine against standard combination therapy.

Future Directions with Growing Emphasis on Translational Research

Moving forward, the committee is focused on new drug development and the integration of novel agents with the most effective treatments that are currently available. Building on the

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results of C9840 that showed the superiority of weekly paclitaxel compared with every 3-weekly therapy, we are comparing nanoparticle, albumin-bound paclitaxel (nab-paclitaxel) with standard paclitaxel in C40502 (18). Patients will also receive bevacizumab based on the recently released results of the pivotal trial from the Eastern Cooperative Oncology Group trial 2100 (20, 21). As part of this planned trial, we have included a number of substudies that will help identify which tumors are most sensitive to these agents and whether surrogate markers can be used to predict response to treatment (22). In addition, there are symptom management and health services questions that will be addressed prospectively. Two trials will evaluate the addition of biological agents to standard endocrine therapy. In C40302, we are comparing fulvestrant alone with fulvestrant plus lapatinib in women whose tumors show some evidence of HER2 expression. In another trial (C40503) for women with hormone receptor–positive metastatic disease, we will compare standard endocrine therapy with the same treatment plus bevacizumab. Each of these trials has been developed to answer correlative questions that will provide a robust understanding of the effect of the investigational agent. This prospective plan to address correlative science questions is an important change from our prior approach, which relied on tissue collection and retrospective development of research goals (see Fig. 1).

Similarly, we are currently assembling a panel of clinical trials that will test novel agents in the preoperative setting. Two trials are in the final stages of development for women with (a) HER2-positive disease and (b) with HER2-negative disease. Expanding on our correlative science focus on HER2, as well as our prominent role in the U.S. Intergroup adjuvant study of trastuzumab, we are planning to test the tyrosine kinase inhibitor lapatinib in the preoperative setting either in conjunction with or in place of trastuzumab. In the HER2-negative setting, we are exploring the use of antiangiogenic therapy with preoperative bevacizumab. These trials will allow us to use in-breast response to more quickly obtain preliminary evidence of efficacy and tissue for correlative science testing. These trials test similar agents and concepts as presently planned for the next generation of adjuvant trials within the North American Intergroup. By launching the preoperative trials before the adjuvant trials, we hope to obtain meaningful data about the clinical effectiveness of the treatments and, more importantly, the potential interactions of the treatments with biological variables. These trials use an investigational agent in an upfront setting, but we are confident in this approach as a result of C8642, which showed the safety of using unproven agents early in the course of treatment.

Conclusion

The Breast Committee of the CALGB has devoted over three decades to the improvement of systemic therapy for patients with all stages of breast cancer. As the summary of work to date shows, we have translated new drug discovery (doxorubicin, paclitaxel, and growth factors) into improved treatment regimens for large numbers of patients. Throughout our history, we have used preclinical models to guide our trial designs. In some cases, as in the case of dose intensification, we rejected the hypothesis that increasing the delivered dose beyond a standard range would improve outcomes. In other cases (i.e., dose density), the preclinical modeling led to clear improvements in disease-free and overall survival. Although there is often a tendency to focus exclusively on the positive results, a well-done study that produces a negative study can be equally important and will push investigators to search for new treatment approaches. Overall, this body of work proved the value of standard doses of doxorubicin, the lack of benefit for higher doses, the use of adding paclitaxel, and the efficacy of shortening intertreatment intervals. The result is more effective and a safer standard chemotherapy for thousands of patients today.

In the years ahead, we are increasing our focus on molecular targets and rational combinations of agents. We plan to leverage the burgeoning knowledge of molecular oncology to inform studies of new targeted agents, and we will use the tissue obtained in this setting to perform laboratory studies to further our knowledge. We expect this to change the treatment of breast cancer profoundly both by dividing the disease into distinct subtypes and by identifying targets for novel therapeutics. Furthermore, we are committed to studies of novel imaging technology to more quickly and accurately identify tumor responses with the expectation that this information will allow for earlier and more precisely tailored therapy for individual patients.

References


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