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Progress on BIG 1-02/IBCSG 27-02/NSABP B-37, a Prospective Randomized Trial Evaluating Chemotherapy after Local Therapy for Isolated Locoregional Recurrences of Breast Cancer

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Background: The utility of chemotherapy for women who experience a locoregional recurrence after primary treatment of early breast cancer remains an open question. An international collaborative trial is being conducted by the Breast International Group (BIG), the International Breast Cancer Study Group (IBCSG), and the National Surgical Adjuvant Breast and Bowel Project (NSABP) to determine the effectiveness of cytotoxic therapy for these patients, either alone or in addition to selective use of hormonal therapy and trastuzumab.

Methods: The trial population includes women who have had a previous diagnosis of invasive breast cancer treated by mastectomy or breast-conserving surgery, but subsequently develop an isolated local and/or regional ipsilateral invasive recurrence. Excision of all macroscopic tumor without evidence of systemic disease is required for study entry. Patients are randomized to receive chemotherapy or no chemotherapy; type of chemotherapy is not protocol-specified. Radiation, hormonal therapy, and trastuzumab are given as appropriate. The primary endpoint is disease-free survival (DFS). Quality-of-life measurements are collected at baseline, and then at 9 and 12 months. The accrual goal is 977 patients.

Results: This report describes the characteristics of the first 99 patients. Sites of recurrence at study entry were: breast (56%), mastectomy scar/chest wall (35%), and regional lymph nodes (9%). Two-thirds of patients have estrogen-receptor-positive recurrences.

Conclusion: This is the only trial actively investigating the question of "adjuvant" chemotherapy in locally recurrent breast cancer. The case mix of accrual to date indicates a broad representation of this patient population.

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The risk of developing metastatic disease is increased among women who develop isolated locore-

gional recurrences following treatment of primary breast cancer.[1] Stage of the index cancer, use of prior adjuvant therapy, and time to recurrence may modulate the prognosis of this patient population.[2–9] Published series report less than 50% 5-year survival in patients experiencing post-mastectomy recurrences and 39–84% 5-year survival in women experiencing ipsilateral breast tumor recurrences after breast-conserving therapy.[2–6,9–19] In a cross-protocol analysis of five National Surgical Adjuvant Breast and Bowel Project (NSABP) node-positive prospective randomized trials, 5-year disease-free survival (DFS) and overall survival (OS) following ipsilateral breast tumor recurrence (IBTR) were 51.4% and 59.9%, respectively.[9] In contrast, patients with other locoregional recurrences (oLRR), excluding IBTRs, fared considerably worse, with 5-year survival of 24.1%.

Three small prospective randomized clinical trials have attempted to test the effectiveness of systemic therapy in patients with locally recurrent breast cancer.[20–22] The Swiss Group for Clinical Cancer Research (SAKK) trial was able to randomize only 50 women with such high-risk tumors to observation versus vincristine, doxorubicin, and cyclophosphamide and closed the study due to the poor accrual with no results reported to date.[23] In the same SAKK trial patients with lower-risk estrogen-receptor-positive (ER+) tumors showed improvement in 5-year DFS if randomized to tamoxifen after radical excision of post-mastectomy recurrences and local radiotherapy of 50 Gy.[10]

An ongoing international multicenter clinical trial (BIG 1-02/IBCSG 27-02/NSABP B-37) is attempting to determine if the substantial risk of systemic relapse following a locoregional recurrence can be reduced by the administration of chemotherapy either alone or in addition to appropriate targeted systemic therapies such as hormonal therapy and trastuzumab. The routine use of alkylating agents, anthracyclines, and/or taxanes as prior adjuvant therapy as well as selective estrogen-receptor modulators and aromatase inhibitors mandates flexibility in the selection of systemic therapies for isolated locoregional relapse. Although it would have been conceptually preferable to restrict possible treatments to a few specific regimens, such a design was impractical given the variety of first-line adjuvant treatments used internationally for adjuvant therapy of breast cancer.

Our intent herein is to describe progress on this clinical trial, to encourage participation, and to increase awareness among surgical oncologists who routinely care for such patients.

METHODS

Study Design and Patient Entry

The trial (BIG 1-02/IBCSG 27-02/NSABP B-37) opened with the Breast International Group (BIG) and International Breast Cancer Study Group (IBCSG) in 2002, and became a collaborative effort with the NSABP in 2005. About half of the patients entered thus far have come from North American centers. This study was approved by the appropriate institutional review committees in accordance with assurances filed with and approved by the Department of Health and Human Services. Written informed consent was required for participation in each trial.

Figure 1 depicts the trial schema. Randomization to either observation (with or without radiation) or chemotherapy (with or without radiation) must take place within 12 weeks of definitive surgical resection of the locoregional recurrence. Patients are stratified according to the use of prior chemotherapy, receptor status [ER- and/or progesterone receptor (PgR)-positive or both negative, as determined by institutional guidelines] of the recurrence, and the location of the recurrence (breast, mastectomy scar/chest wall, or regional lymph nodes).

The trial is open to patients who have developed a histologically proven isolated invasive locoregional recurrence following the treatment of a primary invasive breast cancer.[24] Patients can be enrolled by members of the appropriate groups by accessing the websites of those groups: IBCSG at http://www.ibcsg.org/public/general_pages/trial/open/trial_27-02.shtml; NSABP at http://www.nsabp.pitt.edu/B-37.asp; BIG at http://www.ibcsg27-02_big1-02@ibcsg.org; and by nonmembers through the Clinical Trials Support Unit (CTSU) at http://www.ctsu.org. Patients must have received either breast-conserving therapy or mastectomy for the index cancer and must have had all macroscopic recurrent disease excised. Specifically, margins must be either uninvolved (R0) or only microscopically involved (R1) to meet study selection criteria. Mastectomy or repeat lumpectomy is allowed for patients who received prior lumpectomy.

Only women with histologically proven *first* local and/or regional recurrence of invasive breast cancer on the same side as their primary cancer are considered eligible. Patients may enter the study irrespective of whether lymph node staging surgery or radiation therapy was used in the treatment of the primary breast cancer. Sites of recurrence are defined as: any soft tissue of the ipsilateral conserved breast or the chest wall, mastectomy scar, and/or skin. Regional

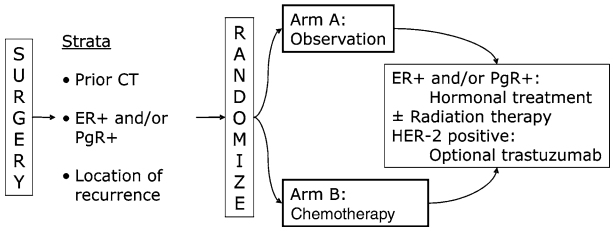

FIG. 1. Schema for the BIG 1-02/IBCSG 27-02/NSABP B-37 study. This figure was previously published in a modified form.[24]

failure is defined as a tumor recurrence in the ipsilateral axillary lymph nodes, extranodal soft tissue of the ipsilateral axilla, and/or ipsilateral internal mammary nodes. Patients with supraclavicular lymph node recurrences, recurrences in the opposite breast, or any evidence of distant disease are not eligible.

Prior to study entry, written informed consent, baseline quality-of-life assessment, and stratification factor information are required. Pathology reports of the primary tumor and recurrence are required. Non-North-American institutions are encouraged to store tumor blocks from both the primary and recurrent tumors for future pathology studies.

Treatment for Locoregional Recurrence

Chemotherapy, if assigned, should begin within 4 weeks of the date of randomization. The choice of chemotherapy drugs, dose adjustments, and use of supportive therapy is left to the discretion of the investigator, but multidrug chemotherapy regimens for at least three cycles or 3 to 6 months are suggested. Estrogen receptor downregulators, aromatase inhibitors, and ovarian suppression are all acceptable alternatives for the required hormonal therapy for estrogen receptor positive (ER+) and/or progesterone positive (PR+) tumors. Adjuvant trastuzumab therapy is allowed for HER-2 overexpressing tumors but can only be administered with chemotherapy if randomized to the chemotherapy arm. Intent to use trastuzumab therapy must be declared prior to randomization.

When radiotherapy is indicated, a dose equivalent to ≥40 Gy is required. Radiotherapy can be administered before, during or after chemotherapy. Patients who develop an IBTR and are treated with mastectomy are not required to undergo radiation therapy even if radiotherapy was not a component of the original breast-conserving therapy. Radiation therapy equivalent to ≥40 Gy is mandatory for all other patients who have not received radiation. For those previously irradiated patients, additional radiation is considered unnecessary if margins of resection are negative (R0). Additional radiation, such as a small-volume boost to the high-risk area is required if margins are microscopically positive. In the latter case, the radiation field must encompass a safety margin beyond the positive margin.

Quality-of-Life Study

The quality-of-life study includes a baseline assessment (before randomization) and assessments at 9 and 12 months after randomization to allow treatment comparisons after chemotherapy is completed. Each assessment includes global linear analog self-assessment (LASA) indicators for physical well-being, mood, coping (PACIS), perceived social support, and subjective health estimation (SHE).[25] LASA indicators specific to symptoms of nausea and vomiting, tiredness, hot flushes, and restrictions in arm movement are also included.

Data Analyses

The primary analysis will be intent-to-treat and the calculated study sample size is 977 patients. Based on previous studies we assume that the overall 5-year DFS for the group receiving no chemotherapy will be 50%. A total of 347 events is required to detect an improvement in 5-year DFS to 60% (hazard ratio 0.74) with 80% power using a two-sided 0.05 level log-rank test. This accounts for two interim analyses during the conduct of the study. To account for nonevaluable cases (5%), the target accrual should be 977 total patients. The outcome measures for efficacy comparisons are DFS, systemic DFS, and OS.

RESULTS

The current report summarizes the clinical–pathological characteristics of the first 99 patients randomized onto BIG 1-02/IBCSG 27-02/NSABP B-37. At study entry most patients had a local recurrence, prior chemotherapy, were postmenopausal, and had hormone-receptor-positive disease (Table 1). The recurrences occurred in the ipsilateral breast in 56%, the mastectomy skin/chest wall in 35%, and in regional lymph nodes in 9% (Fig. 2). Sixty-five percent of patients had received adjuvant chemotherapy. Recurrent tumors were hormone receptor positive by institutional standards in 65% of patients. Table 1

TABLE 1. *Incidence of patient and disease characteristics at study entry*

	Observation	Chemotherapy	Total
Total patients	50	49	99
ER/PgR status			
Negative	18 (36%)	17 (35%)	35 (35%)
Positive	32 (64%)	32 (65%)	64 (65%)
Prior chemotherapy			
No	18 (36%)	17 (35%)	35 (35%)
Yes	32 (64%)	32 (65%)	65 (65%)
Location of primary recurrence			
Breast	27 (54%)	28 (57%)	55 (56%)
Mx scar/chest wall	18 (36%)	17 (35%)	35 (35%)
Regional lymph nodes	5 (10%)	4 (8%)	9 (9%)
Menopausal status			
Pre	11 (26%)	10 (27%)	21 (26%)
Post	32 (74%)	27 (73%)	59 (74%)
Not yet available	7	12	19
Tumor size			
≤2 cm	27 (69%)	24 (67%)	51 (68%)
>2 cm	12 (31%)	12 (33%)	24 (32%)
Not yet available	11	13	24
Age			
30–39 years	5 (10%)	3 (6%)	8 (8%)
40–49 years	10 (20%)	11 (22%)	21 (21%)
50–59 years	19 (38%)	22 (45%)	41 (41%)
60–69 years	10 (20%)	12 (24%)	22 (22%)
≥70 years	6 (12%)	1 (2%)	7 (7%)

ER, estrogen receptor; PgR, progesterone receptor.

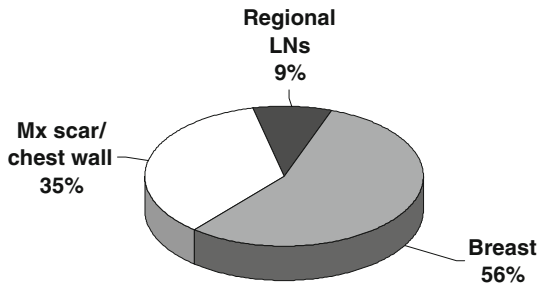

FIG. 2. Sites of locoregional recurrences in the first 99 patients.

shows that the patient and tumor characteristics were balanced according to randomized treatment group.

DISCUSSION

This study represents the last opportunity to formally assess whether chemotherapy adds any benefit to definitive local therapy and systemic targeted therapies for resected, isolated locoregional recurrence of breast cancer. Accrual to this trial has been slower than needed to complete the trial. We recognize that, since isolated locoregional recurrences are infrequent, institutions may have relatively few eligible patients, which can serve as a potential deterrent to activation of the study.

Additionally, in the absence of randomized clinical trial data, patients and physicians have developed biases for or against chemotherapy, which can be a substantial barrier to the successful conduct of scientifically valid trials. Because nearly half the patients entered have chest wall or regional nodal recurrences and over one-third have ER-negative tumors, it is likely that both high- and low-risk cases are being accrued, and thus the trial population is representative of the population at large. BIG 1-02/NSABP B-37/IBCSG 27-02 is an important final effort aimed at providing definitive data needed to evolve evidence-based therapeutic guidelines for patients with isolated invasive recurrences of breast cancer. The trial can only be completed if surgical and medical oncologists commit to the importance of answering the question being addressed and insist the study be opened and supported in their institution even though accrual will be challenging.

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