Multicenter Randomized Clinical Trial of Goserelin Versus Surgical Ovariectomy in Premenopausal Patients With Receptor-Positive Metastatic Breast Cancer: An Intergroup Study

By Charles W. Taylor, Stephanie Green, William S. Dalton, Silvana Martino, Dorothy Rector, James N. Ingle, Nicholas J. Robert, G. Thomas Budd, Jorge C. Paradelo, Ronald B. Natale, James D. Bearden, James A. Mailliard, and C. Kent Osborne

Purpose: **To compare failure-free survival (FFS) and overall survival (OS) for patients with metastatic breast cancer treated with the gonadotropin-releasing hormone (GN-RH) agonist, goserelin versus surgical ovariectomy.**

Patients and Methods: **Between August 1, 1987 and July 15, 1995 138 (136 eligible) premenopausal patients with estrogen receptor (ER)- and/or progesterone receptor (PgR)-positive metastatic breast cancer were entered by the Southwest Oncology Group (SWOG), North Central Cancer Treatment Group (NCCTG), and Eastern Cooperative Oncology Group (ECOG). Prior chemotherapy or hormone therapy for metastatic disease was not allowed. Patients were randomly assigned to goserelin (3.6 mg subcutaneously every 4 weeks; (n = 69) versus surgical ovariectomy (n = 67). The study was initially designed as an equivalence trial with 80% power to rule out a 50% improvement in survival due to ovariectomy. However, accrual was slow and the study was terminated early, which resulted in a final power of 60% for the alternative hypothesis of equal survival distributions.**

Results: **FFS and OS were similar for goserelin and ovariectomy. The goserelin/ovariectomy death hazards ratio was .80 and the associated 95% confidence interval (CI) was .53 to 1.20. The test of 50% improvement in survival due to ovariectomy was rejected at $P = .006$. Goserelin lowered serum estradiol to postmenopausal levels. Hot flashes (75% v 46%) and tumor flare (16% v 3%) were more common with goserelin.**

Conclusion: **Goserelin and ovariectomy resulted in similar FFS and OS. We can rule out a moderate advantage for ovariectomy. Goserelin was safe and well tolerated.**

J Clin Oncol 16:994-999.

APPROXIMATELY 100 YEARS AGO, Beatson[1] reported that endocrine ablation via ovariectomy resulted in regression of skin metastases in breast cancer patients. A number of options for endocrine ablation are currently available, including surgical procedures such as adrenalectomy, ovariectomy, and hypophysectomy; radiation ablation of the ovaries; and, more recently, chemical ablation of ovarian function using gonadotropin-releasing hormone (GN-RH) analogs. Surgical ablation of ovarian function is invasive and irreversible. Response rates to surgical ovarian ablation in premenopausal metastatic breast cancer patients range from 30% to 75%, with higher response rates occurring in patients selected for positive estrogen receptor (ER) and/or progesterone receptor (PgR) status.[2] However, these results also indicate that approximately 50% of premenopausal patients with metastatic breast cancer do not respond to ovarian ablation, even though their tumors may be receptor-positive. Radiation can also effectively reduce ovarian function, and comparative studies with surgical ablation show similar clinical results.[3] However, exposure of patients to pelvic irradiation can make delivery of subsequent palliative chemotherapy more difficult.

The GN-RH analog, goserelin (Zoladex; Zeneca Pharmaceuticals, Wilmington, DE) has been studied in a number of phase II clinical trials in premenopausal patients with

From the University of Arizona, Arizona Cancer Center, Tucson, AZ; Southwest Oncology Group Statistical Center, Seattle, WA; Westlake Comprehensive Breast Center, Westlake Village; University of Southern California School of Medicine, Los Angeles, CA; Mayo Clinic, Rochester, MN; Fairfax Hospital, Falls Church, VA; Cleveland Clinic Foundation, Cleveland, OH; Kansas City Clinical Oncology Program, Kansas City, MO; Spartanburg Community Clinical Oncology Program, Spartanburg, SC; Creighton University Cancer Center, Omaha, NE; and the University of Texas Health Science Center at San Antonio, San Antonio, TX.

Conducted by the Southwest Oncology Group, North Central Cancer Treatment Group, and Eastern Cooperative Oncology Group. Supported in part by the following Public Health Service Cooperative Agreement grant numbers awarded by the National Cancer Institute, Department of Health and Human Services, Bethesda, MD: CA38926, CA21102, CA22433, CA04919, CA35176, CA58882, CA35119, CA37981, CA35431, CA13612, CA46136, CA35281, CA20319, CA35192, CA45450, CA35261, CA35178, CA32734, CA46282, CA27057, CA12213, CA58686, CA46113, CA45560, CA28862, CA52654, CA58861, CA42028, and CA46441.

Address reprint requests to Southwest Oncology Group (SWOG-8692), Operations Office, 14980 Omicron Dr, San Antonio, TX 78245-3217; Email taylor@azcc.arizona.edu.

0732-183X/98/1603-0039$3.00/0

metastatic breast cancer.[4-7] Objective tumor response rates varied from 11% to 45%. Factors that indicated a greater likelihood of response included tumors positive for ER and/or PgR, metastatic disease sites involving soft tissue, and minimal prior chemotherapy or hormone therapy for metastatic disease. Endocrine evaluations of these patients showed goserelin induced a postmenopausal state by altering blood levels of estradiol, luteinizing hormone (LH), and/or follicle-stimulating hormone (FSH). The depot formulation of goserelin allows convenient monthly dosing that enhances patient compliance. Goserelin is generally well tolerated, with the most common side effects being hot flashes and tumor flare reactions.

The primary objective of our study was to compare the failure-free survival (FFS) and overall survival (OS) of premenopausal patients with metastatic breast cancer randomly assigned to treatment with surgical ovariectomy versus monthly goserelin. It was hypothesized that medical treatment with goserelin would be preferred if it was shown to be equivalent or at most only slightly worse than ovariectomy and toxicities were tolerable. Secondary objectives were to compare objective response rates and toxicities of the two treatments and assess the endocrine effects of goserelin by evaluating pretreatment and posttreatment levels of estradiol, LH, and FSH. We were also interested in obtaining information on the response to crossover treatment in patients who failed to respond on their initial treatment arm. The study included strict criteria for confirming premenopausal status, which included required measurements of FSH levels unless patients were unequivocally menstruating regularly. Patients with ER- and/or PgR-positive tumors or those with both ER and PgR status unknown were eligible.

PATIENTS AND METHODS

Patient Eligibility

All patients entered onto this study were informed of the investigational nature of the study and provided written informed consent in accordance with federal and institutional guidelines. Patients were required to have performance status (PS) 0, 1, or 2 according to Southwest Oncology Group (SWOG) criteria. Patients could not have received prior hormone therapy or chemotherapy for metastatic disease. However, patients started on tamoxifen for metastatic disease by their referring physicians were eligible if they had received tamoxifen for no more than 3 weeks and tamoxifen was stopped before study registration. Patients who received prior adjuvant chemotherapy were eligible. Patients who received adjuvant tamoxifen were also eligible if they relapsed ≥6 months after completing tamoxifen therapy.

All patients were required to be premenopausal as defined by one of the following criteria: menstruating actively (< 4 months since last menstrual period [LMP]) or between 4 and 12 months after LMP with a premenopausal FSH level; patients younger than 50 years of age who became amenorrheic while on adjuvant chemotherapy were eligible only if the FSH level was premenopausal; patients younger than 60 years who had a previous hysterectomy (before cessation of menses) with one or both ovaries left intact were eligible if the FSH level was premenopausal. FSH levels were obtained 14 days before registration.

Patients could have measurable, assessable, or nonassessable metastatic breast cancer. Patients with bidimensional lesions by physical examination, x-ray, or computed tomographic (CT) scan were considered to have measurable disease. Patients with bone-only disease manifested by a positive bone scan were considered assessable if they also had bone pain related to bone involvement. Patients with lytic bone disease on x-ray were also assessable. Patients with only a single metastatic lesion smaller than .5 cm, those with malignant pleural effusions or ascites only, and those with asymptomatic bone scan-only disease were considered nonassessable. Nonassessable patients were considered stable until progression. Patients with all evidence of metastatic disease excised were not eligible.

Patients with the following tumor hormone receptor characteristics were eligible: ER-positive (≥ 3 fmol/mg cytosol protein or positive by institutional standards), PgR-positive (≥ 5 fmol/mg cytosol protein or positive by institutional standards), or ER and PgR results unknown and no accessible tumor tissue for biopsy. Receptor status could be assayed either on the original primary tumor or on metastatic tumor at the time of relapse. Hormone receptor assays by immunohistochemical methods were acceptable.

Patients with life-threatening progressive disease in brain, liver, or lung in whom it was felt chemotherapy would result in a more rapid and beneficial response were ineligible. Patients with extensive liver metastases (> one third the mass of the liver) or lymphangitic lung metastases were not eligible. Patients with existing nonmalignant disease that would result in increased anesthesia risk or other contraindication to surgical ovariectomy were not eligible. Pregnant patients were not eligible. While on study with goserelin, barrier contraception was required. Patients were required to be free of all nonbreast cancers at the time of registration and free of any nonskin cancers for at least 5 years.

Efficacy and Safety Evaluation

History, physical examination, weight, performance status, documentation of tumor measurements by physical examination, and toxicity evaluations were performed in each patient prestudy and repeated monthly while on study. The ER and PgR status of each patient's tumor was documented prestudy. LH, FSH, and serum estradiol levels were performed prestudy in patients who received goserelin and repeated after 8 weeks of therapy with goserelin. Complete blood cell count and determination of creatinine, alkaline phosphatase, calcium, AST, lactate dehydrogenase (LDH), and bilirubin levels were performed prestudy and repeated every 3 months. Chest x-ray and bone scan were required prestudy. Bony sites positive on bone scan were evaluated with bone x-rays. Patients with clinical suspicion of liver metastases or abnormal liver functions were required to have radionuclide or CT scans of the liver prestudy. X-rays and scans used for tumor assessment were repeated every 3 months. The operative report for ovariectomy patients was submitted no more than 2 weeks following the procedure. Following removal from study, patients were evaluated for survival every 6 months.

Treatment Plan

Goserelin (Zoladex) was supplied as a 3.6-mg depot formulation preloaded in a disposable syringe. Goserelin (3.6 mg) was administered by subcutaneous injection every 4 weeks. The dose could be increased to two depots (total of 7.2 mg of goserelin) into different sites every 4 weeks if after 8 weeks the patient had not become amenorrheic and

serum estradiol levels were not in the menopausal range. Surgical ovariectomy was performed using standard surgical procedures. Patients remained on protocol treatment until time of progression, death, or patient wishes.

Patients with clear progression at least 6 weeks following ovariectomy were offered crossover to goserelin if they continued to meet the original eligibility criteria (with the exception of being premenopausal). Patients who progressed at least 6 weeks following crossover to goserelin were removed from study. Likewise, patients with clearly progressive disease after at least 6 weeks of initial treatment with goserelin were offered crossover to ovariectomy if they continued to meet the original eligibility criteria. Patients who developed progressive disease following crossover to ovariectomy were removed from the study. A limited number of patients were treated by crossover, as it was only offered during the early portion of the trial (see Statistical Considerations).

Response Criteria

Previously reported SWOG response criteria were used in this study.[8] Additional criteria were used for patients with assessable bone disease. For patients with bone metastases and a complete response (CR) in other assessable sites of disease, normalization of involved skeleton was not required, but skeletal survey and/or bone scan had to be clearly improved. For patients with bone-only disease, CR required all lytic lesions to be remineralized by x-ray and bone scan normalized with no new lesions and the patient could have no bone pain (off analgesics) and no further pathologic fractures. For patients with bone-only disease, a partial response (PR) required complete disappearance of bone pain accompanied by an unequivocal decrease in size and density of bone lesions on x-ray or bone scan with no new lesions.

Patients with bone scan-only disease or blastic bone disease were designated improved if the bone scan remained stable and bone pain improved or PS improved by at least one level. Stable disease indicated no change in measurable bone lesions with no deterioration in PS and no worsening of pain (increased pain due to tumor flare in the first 2 weeks of therapy not included).

Statistical Considerations

The primary objective of this study was to assess differences in survival in premenopausal patients whose first treatment for metastatic disease was medical castration using goserelin, versus those whose first treatment was surgical castration. It was assumed that medical treatment with goserelin would be the preferred method of treatment if goserelin was shown to be equivalent or at most only slightly worse than ovariectomy and toxicities were tolerable. Therefore, the study was designed as an equivalence trial. The null hypothesis (H_0) was that ovariectomy would result in 50% improvement in survival, with the alternative hypothesis (H_1) being that the survival distributions for patients treated with goserelin versus ovariectomy were equal. It was anticipated that 40 patients per year would be accrued to the study and that a maximum of 5 years would be necessary to accrue 200 patients (100 patients per treatment arm). This design would have resulted in 80% power to reject the hypothesis that survival with ovariectomy was 50% or better than that with goserelin. However, accrual to the study was slower than expected and after approximately 8 years of accrual, 136 eligible patients had been entered (69 randomized to goserelin and 67 randomized to ovariectomy). After consideration by the SWOG Data Monitoring Committee, it was decided to terminate the study early, which resulted in a final power of 60% for the alternative hypothesis of equal survival distributions.

All patients were registered through the SWOG Statistical Center. Stratification factors included measurable versus assessable bone versus other, soft tissue and/or bone versus visceral disease, and subgroups of the cooperative groups involved (Community Clinical Oncology Program [CCOP] *v* Cooperative Group Outreach Program [CGOP] *v* member institution). A dynamic allocation scheme was used to randomize patients to the two treatments. Treatment arms were balanced on the stratification factors within subgroups of institutions. Descriptive factors included PS (0 to 1 *v* 2) and prior adjuvant tamoxifen (yes *v* no). Criteria for removal of a patient from goserelin treatment included toxicity unacceptable to the patient or the treating physician, patient wishes, or progression of disease. The criteria for removal of a patient from the ovariectomy arm included patient wishes or progression of disease.

Response to treatment was assessed in patients with measurable disease and assessable bone disease. Time to treatment failure was measured from the date of randomization to the date of first documentation of progression, death, or off treatment (off goserelin for patients on the goserelin arm; initiation of new treatment for patients on the ovariectomy arm). Survival was calculated from the date of randomization to the date of death.

Crossover to goserelin or ovariectomy was planned as a small phase II type evaluation of these modalities after initial failure. The plan was to accrue initially 10 patients to each arm and then close an arm if there were no responses or continue accrual to 20 patients if there was at least one response. The actual number of patients crossed over varied slightly from this plan, because registrations continued for a short time after the closure notice went out to accommodate patients who had already been offered or instituted crossover treatment. It was considered that five or more responses among 20 patients would be of further interest.

RESULTS

Between August 1, 1987 and July 15, 1995 138 patients were registered for this study. One patient on the ovariectomy arm was ineligible due to preoperative FSH level in the postmenopausal range. One patient on the goserelin arm was ineligible due to insufficient information submitted to determine eligibility. Thus, 136 patients were randomized: 69-goserelin patients and 67-ovariectomy patients. There were four major protocol deviations: three on the ovariectomy arm and one on the goserelin arm. These patients are included in this analysis. Two patients randomized to ovariectomy did not undergo surgery (not performed due to risk of bowel injury and due to incomplete initial evaluation) and one had inadequate surgery (continued to menstruate following ovariectomy). The one patient on the goserelin arm received one dose of treatment and no further follow-up evaluation. Seven additional patients with measurable or assessable disease were considered not assessable for response due to inadequate baseline disease assessment. These patients were otherwise eligible and are included in all other analyses.

The clinical characteristics of the patients randomized to goserelin versus ovariectomy were closely balanced (Table 1). The majority had PS 0 or 1 and few had received tamoxifen in the adjuvant setting. The percentage of patients with measurable disease was similar between the two arms. Slightly more patients in the goserelin arm had nonassessable disease (20% *v* 9%) and slightly more patients in the

Table 1. Patient Characteristics

Characteristic	% of Patients	
	Goserelin (n = 69)	Ovariectomy (n = 67)
Age, years		
Median	41	40
Range	26-54	26-55
Race		
White	87	87
Black	9	9
Other	4	4
Institution		
Member	58	55
CCOP	32	34
CGOP	10	10
Disease status		
Measurable	42	46
Assessable bone	38	45
Nonassessable	20	9
Dominant Sites		
Soft tissue/bone	71	69
Visceral	29	31
PS		
0-1	93	97
2	7	3
Hormone receptors		
ER+/PgR+	86	81
ER+/PgR−	6	10
ER+/PgR unknown	4	4
ER−/PgR+	3	3
ER/PgR both unknown	1	2
Prior adjuvant tamoxifen		
Yes	1	6
No	99	94

ovariectomy arm had assessable bone disease (45% *v* 38%). However, the two groups were well balanced for prognosis as it relates to disease sites (soft tissue and bone *v* visceral) and hormone receptor status.

The overall response rate (CRs plus PRs) was 31% for patients with measurable disease randomized to goserelin and 27% for patients with measurable disease randomized to ovariectomy (Table 2). The CR rate was low in both treatment arms: goserelin, 14%; and ovariectomy, 10%. The differences in response rates between the two treatment arms were not statistically significant. Due to the large number of patients with bone-only and nonassessable disease (Table 1),

Table 2. Treatment Respone

Response	Measurable Disease			
	Goserelin (n = 29)		Ovariectomy (n = 30)	
	No.	%	No.	%
CR	4	14	3	10
PR	5	17	5	17
Stable disease	8	28	8	26
Increased disease	7	24	9	30
Inadequate assessment	5	17	5	17

objective antitumor response was difficult to assess for the group as a whole. Only two responses in patients with assessable bone disease were recorded, both on goserelin.

FFS was not significantly different between the ovariectomy and goserelin treatment arms (goserelin/ovariectomy failure hazards ratio, .73; 95% confidence interval [CI], .51 to 1.04) (Fig 1). The test of a 50% improvement in FFS due to ovariectomy was rejected at P less than .001. The median FFS for the ovariectomy and goserelin groups was 4 and 6 months, respectively. Likewise, OS was not significantly different between the two groups (goserelin/ovariectomy death hazards ratio, .80; 95% CI, .53 to 1.20) (Fig 2). The test of a 50% improvement in survival due to ovariectomy was rejected at $P = .006$. The median OS for the ovariectomy and goserelin groups was 33 and 37 months, respectively. By multivariate analysis, the presence of measurable disease, age (< 40 *v* > 40 years), disease-free interval (< 3 *v* > 3 years), PS (0 *v* 1 or 2), and PgR negativity were not associated with survival. However, site of disease (visceral *v* nonvisceral) was associated with OS ($P < .001$) and FFS ($P = .05$).

A small number of patients who failed to respond to treatment on their initial assigned treatment arm but continued to meet the eligibility requirements were crossed over to the opposite treatment arm. Nineteen patients were crossed over to ovariectomy (13 with measurable disease) and 15 were crossed over to goserelin (nine with measurable disease). There were no major protocol deviations in the crossover treatments. However, four patients crossed over to goserelin received only one injection due to rapid progression of disease. Among all crossover patients, only one response in the patients with measurable disease was documented: a CR following crossover to ovariectomy. Neither group had a sufficient number of responses to be of further interest.

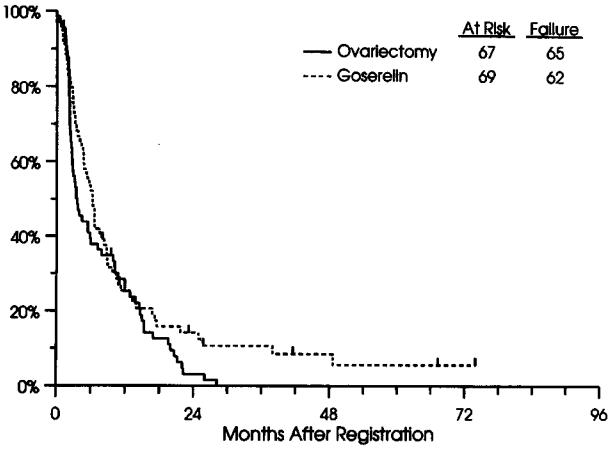

Fig 1. FFS by treatment arm.

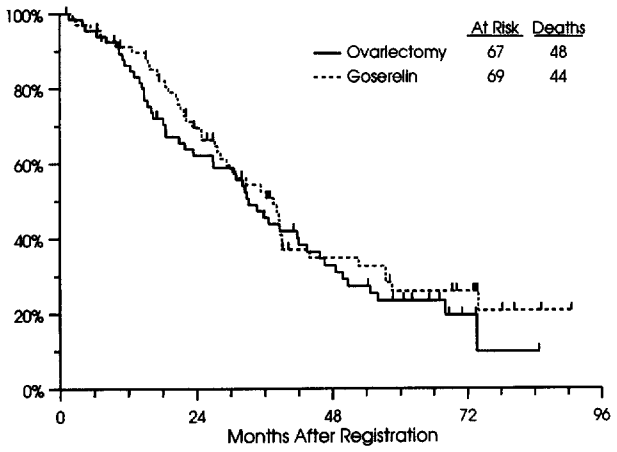

Fig 2. OS by treatment arm.

Table 3 lists baseline estradiol, LH, and FSH values for patients randomized to goserelin. Paired follow-up data after 8 weeks (two injections) of goserelin therapy were available for estradiol in 33 patients, LH in 36, and FSH in 38. In general, the mean values of estradiol, LH, and FSH decreased by week 8, which indicates goserelin induced a postmenopausal state in these patients. The median change (week 8 minus baseline values) for estradiol was − 96 (range, − 394 to + 12), for LH was − 11 (range, − 129 to + 31), and for FSH was − 9 (range, − 184 to + 68). Similar data are not available for patients on the ovariectomy arm.

Treatment with goserelin was generally well tolerated. Grade 1 and 2 adverse events (SWOG toxicity criteria) for goserelin and ovariectomy patients are compared in Table 4. Grade 3 toxicities were rare and included bone pain (0% on the goserelin arm, 2% on the ovariectomy arm), hot flashes (9% and 3%, respectively), malaise (2% and 0%), personality change (2% and 0%), thrombocytopenia (2% and 0%), and vision change (2% and 0%). Only one grade 4 toxicity was observed: grade 4 leukopenia in a patient on goserelin. There were no treatment-related deaths. Hot flashes ($P = .001$) and tumor flare reactions ($P = .01$) were significantly more common with goserelin. Toxicity reporting may have been more complete for goserelin patients, because they were required to return monthly for treatment.

Table 3. Endocrine Profiles For Goserelin Patients

Variable	Estradiol (pg/mL)	LH (IU/L)	FSH (IU/L)
No. of patients	33	36	38
Mean baseline level	117.4	16.1	18.3
Mean week 8 level	21.6	5.5	9.7

Table 4. Grade 1 and 2 Adverse Events (> 5% of patients)

	Goserelin (n = 68)*		Ovariectomy (n = 65)†	
Adverse Event	No.	%	No.	%
Hot flashes	45	66	28	43
Tumor flare	11	16	2	3
Bone pain	4	6	2	3
Leukopenia	6	9	1	2
Nausea	7	10	4	6
Edema	5	7	0	0
Malaise	4	6	1	2
Sweats	4	6	2	3
Vomiting	2	3	4	6

*One patient (of 69) who received only 1 dose of goserelin and no further follow-up evaluation is not included in these toxicity data.

†Two patients (of 67) who did not undergo surgery (due to risk of bowel injury and incomplete initial evaluation) are not included in these toxicity data.

DISCUSSION

This study accrued 136 eligible patients over an interval of approximately 8 years and randomized them to receive goserelin versus surgical ovariectomy as treatment for receptor-positive, metastatic breast cancer. No significant differences were observed in FFS or OS between the two treatment groups. For patients with measurable disease, CR and PR rates were low in both the goserelin (31%) and ovariectomy groups (27%). However, due to the large number of patients with bone-only or nonassessable disease, objective responses were difficult to determine accurately and survival duration is a more accurate indicator of benefit for patients on this study. Both treatments were well tolerated, with goserelin resulting in slightly more hot flashes and tumor flare reactions.

In the design of this study, it was appreciated that accrual could require a long time due to the strict entry requirements for premenopausal patients with ER- and/or PgR-positive tumors and no prior treatment for metastatic disease. Accrual was also anticipated to be slowed by difficulties in patient acceptance of randomization between a surgical procedure and a drug treatment.

In premenopausal patients with hormone receptor-positive breast cancer, there is good rationale for treatment with endocrine ablation. Endocrine ablation may be achieved by surgically removing the ovaries or using medical castration to interrupt the pituitary-ovarian axis, which results in suppression of estrogen production. Surgical ovariectomy has been used for the last 100 years as treatment for metastatic breast cancer in premenopausal patients. In an overview analysis, ovarian ablation in the adjuvant setting resulted in OS benefit in younger women.[9] With the availability of drugs, such as goserelin, that could safely result in reversible ovarian ablation without requiring a surgical procedure and in response rates similar to ovariectomy in phase II trials, a randomized comparison was

warranted. Additionally, we believed it was necessary to pursue a randomized comparison because of the possibility that the ovary could produce breast cancer growth factors that might not be suppressed by GN-RH agonists such as goserelin. Indeed, in patients who have achieved medical castration with amenorrhea from chemotherapy using cyclophosphamide, methotrexate, and fluorouracil (CMF), significant responses can still occur with surgical ovariectomy for recurrent disease.[10] Furthermore, ovarian ablation is permanent and could theoretically affect survival after disease progression.

Tamoxifen has also been used to treat premenopausal patients with metastatic breast cancer,[2] and two randomized comparisons of surgical ovariectomy versus tamoxifen have been reported.[11,12] These studies illustrate some of the difficulties of pursuing randomized trials in this clinical circumstance. Buchanan et al[12] randomized 122 premenopausal patients with advanced local, locally recurrent, or metastatic breast cancer to receive tamoxifen versus surgical ovariectomy. Although all patients were well documented to be premenopausal (regular menstruation or premenopausal FSH), ER- and/or PgR-positive tumor status was not an entry requirement. ER status was unknown in 54% of the entire group, while 25% were ER-positive and 21% were ER-negative. No significant differences were observed in response rate, duration of response, or OS. Approximately 4 years were required for accrual to this study and the power to detect a 50% improvement in one treatment was only .33.[2]

Ingle et al[11] entered 53 premenopausal patients with metastatic breast cancer over 6 years and randomized them to receive surgical ovariectomy versus tamoxifen. Menopausal status was not assessed by estradiol or FSH levels, and ER status was unknown in 19% of patients randomized to ovariectomy and 23% of patients randomized to tamoxifen. There were no statistically significant differences in time to progression or OS. This study had a power of only .22 to rule out a 50% improvement by one treatment.[2]

It is recognized that studies such as ours that are designed to show equivalence between two treatments will require larger numbers of patients for adequate power than comparative trials designed to show one treatment is significantly better than another.[13] Trials that are designed to show a difference between treatments commonly require fewer patients because they are generally designed to have power only for large differences. With this in mind, our trial was designed as an equivalence trial from the beginning, but slow accrual prevented achievement of the original accrual goals. Despite the difficulties due to slow patient accrual, our study remains the largest randomized comparative trial of surgical ovarian ablation versus chemical ovarian ablation reported to date. Since the time our study was originally designed (~1985), surgical techniques for ovariectomy have evolved and the procedure can now be performed with less cost and morbidity using laparoscopic techniques. Our results allow us to rule out at least a moderate advantage for surgical ovariectomy over goserelin. Thus, our study allows patients and physicians to rationally choose between an invasive and permanent surgical procedure versus a reversible drug treatment, both of which result in similar clinical benefit.

ACKNOWLEDGMENT

We acknowledge Patti Waldman for excellent data management for this clinical trial.

REFERENCES

1. Beatson GT: On the treatment of inoperable cases of carcinoma of the mamma: Suggestions for a new method of treatment with illustrative cases. Lancet 2:104-107, 1996

2. Sunderland MC, Osborne CK: Tamoxifen in premenopausal patients with metastatic breast cancer: A review. J Clin Oncol 9:1283-1297, 1991

3. Stoll BA: Palliation of breast cancer by castration or by hormone administration, in Stoll BA (ed): Breast Cancer Management—Early and Late. London, United Kingdom, Heinemann Medical, 1977, pp 143-146

4. Saphner T, Troxel AB, Tormey DC, et al: Phase II study of goserelin for patients with postmenopausal metastatic breast cancer. J Clin Oncol 11:1529-1535, 1993

5. Bajetta E, Celio L, Zilembo N, et al: Ovarian function suppression with the gonadotrophin-releasing hormone (GnRH) analogue goserelin in premenopausal advanced breast cancer. Tumori 80:28-32, 1994

6. Brambilla C, Escobedo A, Artioli R, et al: Medical castration with Zoladex: A conservative approach to premenopausal breast cancer. Tumori 77:145-150, 1991

7. Bajetta E, Zilembo N, Buzzoni R, et al: Goserelin in premenopausal advanced breast cancer: Clinical and endocrine evaluation of responsive patients. Oncology 51:262-269, 1994

8. Green S, Weiss GR: Southwest Oncology Group standard response criteria, endpoint definitions and toxicity criteria. Invest New Drugs 10:239-253, 1992

9. Early Breast Cancer Trialists' Collaborative Group: Systemic treatment of early breast cancer by hormonal cytotoxic or immune therapy: 133 randomized trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Lancet 339:1-15-71-85, 1992

10. Bonnadonna G, Volagussa P, Rossi A, et al: CMF adjuvant chemotherapy in operable breast cancer, in Junes SE, Salmon SE (eds): Adjuvant Therapy of Cancer II. New York, NY, Grune & Stratton, 1979, pp 227-235

11. Ingle JN, Krook JE, Green SJ, et al: Randomized trial of bilateral oophorectomy versus tamoxifen in premenopausal women with metastatic breast cancer. J Clin Oncol 4:178-185, 1986

12. Buchanan RB, Blamey RW, Durrant KR, et al: A randomized comparison of tamoxifen with surgical oophorectomy in premenopausal patients with advanced breast cancer. J Clin Oncol 4:1326-1330, 1986

13. Makuch RW, Johnson MF: Some issues in the design and interpretation of 'negative' clinical studies. Arch Intern Med 146:986-989, 1986