

Hormone Replacement Therapy in Previously Treated Breast Cancer Patients

Alan G. Wile, MD, FACS, Richard W. Opfell†, MD, David A. Margileth, MD, Orange, California

We report our experience with 25 women previously treated for breast cancer who subsequently received hormone replacement therapy (HRT) for the relief of menopausal symptoms and the prevention of postmenopausal cardiovascular disease and osteoporosis. Two patients had *in situ* disease, 13 had stage I disease, 7 had stage II disease, 1 had stage III disease, and 2 had invasive cancer of undetermined stage. Seventeen patients (group I) began HRT less than 24 months after primary breast cancer therapy, and 8 patients (group II) began HRT more than 24 months after breast cancer therapy. The HRT-free interval for group I patients averaged 7.9 months and for group II patients averaged 64.5 months. The average period of observation while receiving HRT for the entire group was 35.2 months (range: 24 to 82 months). Three of 25 patients have had a recurrence, all in group I. One patient developed local recurrence after breast conservation treatment, and her condition was salvaged by further wide excision. Two patients developed recurrence after mastectomy, and one patient ultimately died of systemic disease. The overall survival rate for the entire group was 96%. Overall survival of high-risk group I patients, with a mean follow-up of 30.4 months, was 94%. We recognize that this report of HRT in a small group of patients does not have the power to demonstrate an adverse effect of HRT on breast cancer. However, the lack of an obvious adverse effect of HRT in this group of breast cancer patients and the known beneficial effect of HRT on postmenopausal cardiovascular disease and osteoporosis warrant formal prospective trials of HRT in such patients.

Hormone replacement therapy (HRT) is effective in relieving the signs and symptoms of menopause. HRT has demonstrated substantial improvement in the patient's quality of life and survival as a result of the prevention of osteoporosis and cardiovascular disease [1-3]. Previously treated breast cancer patients have been denied the beneficial effects of HRT because of the beliefs that renewed hormonal exposure would accelerate the growth of occult breast cancer or facilitate breast carcinogenesis. These conclusions were drawn from observations that have been proven to be erroneous. For example, the observation that pregnant breast cancer patients fared worse than nonpregnant breast cancer patients was held to be due to the stimulation of the cancer by placental estrogens. It has been demonstrated that the youth of the pregnant patients and the advanced stage of disease, rather than the pregnancy, confer the unfavorable prognosis on these patients [4]. Nevertheless, the poor outcome in pregnant breast cancer patients was a cornerstone upon which the recommendation to avoid hormone exposure in previously treated breast cancer patients was based. Situations in which breast cancer and estrogen exposure (pregnancy, oral contraceptives, HRT) coincide were reviewed [5]. Concurrent or subsequent exposure to estrogens either had no effect or a beneficial effect on the outcome of breast cancer patients.

A number of breast cancer patients under our care have requested HRT after the treatment of their cancer. We were aware of the traditional recommendations against the use of HRT in such patients. Certain patients were persistent in requesting this treatment either because of severe menopausal symptoms or because of their fear of developing cardiovascular disease and osteoporosis. Our review of those situations in which HRT and breast cancer co-existed did not suggest an adverse effect of HRT upon previously treated breast cancer patients. Furthermore, there had been no prior reports of HRT administered to such patients upon which to base recommendations. The absence of information incriminating HRT in these patients combined with the strong desire on the part of the patients for this treatment resulted in patients who were cancer-free receiving HRT. This report details our favorable experience with HRT in a select group of menopausal breast cancer patients.

Patients were treated at UC Irvine Medical Center and St. Josephs' Hospital of Orange, California. Thirteen patients underwent definitive primary therapy at UC Irvine and were observed (AGW). Ten were receiving treatment at St. Josephs' Hospital (RWO, DAM). Two others were referred to UC Irvine specifically for HRT. Efforts were made to exclude patients with recurrent or residual breast cancer. The unconventional practice of prescribing HRT to previously treated breast cancer pa-

From the Department of Surgery, UC Irvine, the St. Josephs' Hospital Cancer Center, and the Breast Care Center of Orange County, Orange, California.

†Deceased.

Requests for reprints should be addressed to Alan G. Wile, MD, Department of Surgery, UC Irvine Medical Center, 101 City Drive South, Orange, California 92668.

Manuscript submitted January 30, 1992, and accepted in revised form June 9, 1992.

tients was emphasized. It was stated that the known beneficial effects of HRT should be weighed against the uncertain effect of HRT on breast cancer. Patients were told that possible effects include the exacerbation of the previous breast cancer, no effect on that breast cancer, or a beneficial effect upon the breast cancer. Those patients electing HRT were generally referred to gynecologists at our institutions willing to prescribe HRT with documentation from us. Several patients had undergone total abdominal hysterectomy with bilateral salpingo-oophorectomy and had HRT prescribed by us without referral to a gynecologist. The specific regimen of HRT was the responsibility of the gynecologist or the treating oncologist. As a result, the regimens varied in content and also with time as physicians altered regimens to treat specific symptoms. Typical regimens consisted of conjugated estrogens (0.625 to 1.25 mg) with or without progesterone. One patient received estradiol by means of a transdermal patch.

Early on, we were more comfortable allowing HRT in patients with early breast cancer with a disease-free period. Later, we no longer insisted on a disease-free interval between definitive primary therapy for breast cancer and the initiation of HRT. Also, we allowed patients with a more advanced stage of disease at diagnosis to receive HRT.

Twenty-five women with previously treated breast cancer requested and received HRT. The range in age at diagnosis was 39 to 67 years (mean: 51 years). The stage of disease and the mode of primary therapy are listed in Table I. The disease-free interval between primary therapy and the start of HRT averaged 26.0 months (range: 0 to 180 months). The entire group was subdivided into two groups. Group I included 17 patients who began HRT soon (less than 24 months) after primary therapy for breast cancer. In this group, the average interval between primary therapy and the initiation of HRT was 7.9 months. In group II, eight patients underwent therapy for breast cancer in the past (more than 24 months) and either recently became menopausal or recently sought relief of menopausal symptoms. The average disease-free interval between primary therapy and HRT for this group was 64.5 months. Five patients began HRT immediately upon completion of definitive primary therapy (no disease-free interval). Three women received HRT prior to the diagnosis of breast cancer. Two of these patients continued HRT after breast cancer treatment. Of the 16 patients in whom estrogen receptor (ER) status was determined, 13 (81%) were positive.

One woman had local recurrence after breast conservation therapy and prior to beginning HRT. She received four doses of external beam radiation and then discontinued radiation. She had multiple local recurrences excised over a 5-year period before undergoing mastectomy. She is listed in Table I as a stage II mastectomy patient. This patient began HRT immediately after mastectomy.

The average duration of treatment of all patients with HRT is 35.2 months as of November 1, 1991 (range: 6 to 78 months). No patients have been lost to follow-up. The average duration of treatment for group I patients was

TABLE I
Stage of Disease and Mode of Primary Therapy

	No (%)	Mastectomy	Breast Conservation
Stage			
0	2 (8)	0	2
I	13 (52)	2	11
II	7 (28)	4	3
III	1 (4)	0	1
IV	0	—	—
Unknown	2 (8)	2	0
Total	25	8	17

30.4 months and for group II patients was 45.6 months. Three patients have had recurrences during the observation period while receiving HRT. All three were in group I. One patient underwent wide excision at another hospital of what was thought to be ductal carcinoma *in situ* and axillary dissection. Review of the breast tissue several years later demonstrated that invasive ductal cancer had been present. Forty-seven months after the initiation of HRT, this patient developed local recurrence, which was treated by wide local excision, and she still receives HRT. She continues to be disease-free at the present time. The second patient to have a recurrence underwent mastectomy for a stage I breast cancer (ER-/PR+ [progesterone receptor]). The interval between mastectomy and initiation of HRT was 14 months. She began HRT and developed systemic recurrence 6 months later when HRT was discontinued. She died 6 months after the recurrence was first detected. This was the only patient to die of any cause during the observation period, yielding an overall survival rate of 96%. The third patient has recently developed local recurrence 4.5 years after a mastectomy for a T2N0M0 ER+ breast cancer. There was an interval of 14 months between the mastectomy and initiation of HRT. The patient was observed while receiving HRT for 41 months until the local recurrence was discovered.

A fourth patient underwent breast conservation treatment. She received HRT from her physicians for relief of menopausal symptoms. She developed local recurrence 2 years later, underwent mastectomy, and was not permitted to continue HRT. She remained disease-free, was seen by us 4 years later, began HRT for a second time, and remains disease-free. She was classified as a group II patient since more than 2 years had elapsed between mastectomy and the initiation of HRT by us.

Two patients had positive nodes. One had a disease-free interval of nearly 7.5 years prior to beginning HRT. The other patient is a woman who was diagnosed with a T4N1M0 breast cancer at age 42 years. She underwent adjunctive chemotherapy and had amenorrhea accompanied by typical menopausal symptoms. After an interval of 20 months, she began HRT. Both women remain disease-free with a duration of observation while receiving HRT of 50 and 35 months, respectively.

No formal effort was made to document the quality of life in this group of patients. However, patients were

asked about the effect of HRT upon the quality of their lives. Group II patients generally stated that, after HRT, their menopausal symptoms abated and their quality of life resembled that prior to breast cancer therapy. The younger patients generally expressed relief that HRT would largely reduce their risk of osteoporosis and cardiovascular disease.

Patients in this report can be best discussed based on the length of time between definitive primary therapy and the initiation of HRT. The majority of these patients (group I) had a disease-free interval of less than 24 months. This length of time is significant in that the majority of recurrences will occur within 2 years of diagnosis. Group I patients are at relatively high risk for recurrence. The probability of recurrence declines as the length of time from diagnosis increases. Group II patients with a disease-free interval averaging 64.5 months were very unlikely to experience a recurrence.

The purpose of this report was to begin to address the issue of the safety of HRT in women previously treated for breast cancer. The Kaplan-Meier estimate for cumulative survival at 2 years of 96% overall and 94% for group I patients with a mean follow-up of 30 months supports the safety of HRT in this setting. Although group I includes two patients with *in situ* disease, it also includes four patients with stage II disease and one patient with stage III disease. The only patient to receive adjunctive medication that might have delayed recurrence was the patient with stage III disease who received cytotoxic chemotherapy.

Three patients developed recurrence while receiving HRT under our supervision. A fourth developed local recurrence while receiving HRT prior to our involvement but restarted HRT under our care. One patient developed local recurrence after what would be considered inadequate local therapy for an invasive breast cancer. The recurrence would have been expected. The second patient with local recurrence after mastectomy discontinued the HRT and has begun receiving tamoxifen. It will be interesting to see whether this patient's cancer, which progressed during HRT, will respond to tamoxifen. A single patient died 26 months after mastectomy for a T1N0M0 breast cancer after receiving HRT for 6 months. Taken in context with the other 24 breast cancer patients, this single cancer-related death does not address either the safety or the risk of HRT in previously treated breast cancer patients.

One might question the aspects of HRT administration in previously treated breast cancer patients. If the first 2 years after cancer diagnosis represent the greatest risk period, then why not wait 2 years before initiating HRT? If the ER status is known and the patients are ER-negative, presumably unresponsive to hormones, then why not administer HRT to ER-negative patients only? In response to these questions, many patients in the study were constantly symptomatic prior to beginning HRT. These patients strongly preferred to accept a theoretic increased risk of recurrent breast cancer rather than delay initiation of HRT for a significant period of time. It is known that certain consequences of menopause, particu-

larly loss of bone mineral density, occur most rapidly at menopause, with declining rates of bone density over time. A last point remains unresolved, the potential beneficial effect of HRT upon the previously treated breast cancer. This is a possibility that should be evaluated in future studies. If no effect or a beneficial effect upon breast cancer recurrence is demonstrated, then there would be no reason to delay the initiation of HRT.

Whether ER-positive patients should receive HRT touches upon the confusion regarding the relationship of estrogens and breast cancer. Estrogens have two effects with respect to breast cancer. The first is related to carcinogenesis. Our current understanding of carcinogenesis is described by a two-stage model of initiation followed by promotion. Initiation may be caused by radiation, chemicals, viruses, or other agents and occurs over a brief period of time. Promotion is the second step in carcinogenesis and requires a long exposure to a second substance (promoter), which, by itself, may be innocuous. In breast cancer, the promoter is probably estrogen. In animal models of breast carcinogenesis, estradiol is the most potent promoter. Non-estradiol estrogens are either weak promoters or function as anti-promoters and protect against carcinogenesis [6]. In this country, conjugated estrogens are the most frequently administered medications for HRT. The majority of estrogens in conjugated estrogens are non-estradiol estrogens. If analogous to the animal model, then HRT may have little, if any, harmful effect with respect to breast carcinogenesis and may even function as an anti-promoter providing protection against development of second primary breast cancers.

The second effect of estrogen upon breast cancer is that it functions as a growth factor. Estradiol is the most potent growth factor. Any estrogen that binds with the estrogen receptor and competes with estradiol inhibits tumor growth for receptor-positive tumors. Estrogens are considered potent when they manifest systemic estrogenic effects. Diethylstilbestrol (DES) is a potent estrogen with good anti-breast cancer effects. Recently, tamoxifen has replaced DES as the antagonist of choice in breast cancer therapy because of the relative absence of systemic estrogen effects. However, tamoxifen may be defined as an estrogen because of its affinity for the ER receptor and its mild estrogenic effects on bone density [7] and serum lipids [8]. The use of tamoxifen in breast cancer supports the use of other non-estradiol estrogens such as conjugated estrogens. Conjugated estrogens have been used successfully to treat recurrent breast cancer [9]. Women receiving HRT at the time of breast cancer diagnosis have a significant 5-year survival advantage when compared with nonusers at the time of their diagnosis, which further supports the use of HRT in previously treated breast cancer patients [10].

We strongly believe that this report should not be interpreted as demonstrating the safety of HRT in previously treated breast cancer patients. The ability to detect an adverse effect of HRT on breast cancer in this small group of patients is very slight. Had we detected early and uncontrolled recurrence in a substantial number of patients, these results would have been reported, and no

further investigation would have been recommended. In light of our findings, we recommend expanded, formalized studies in a prospective setting. The incidence of breast cancer continues to increase such that it will be the most frequently diagnosed internal cancer in the United States in 1993. Cytotoxic chemotherapy is being used more frequently in young women, resulting in chemotherapy-induced menopause. The proportion of women cured of breast cancer continues to increase, accompanied by a general increase in longevity. The result is ever-increasing numbers of women previously treated for breast cancer who become menopausal and candidates for HRT. Based upon the known beneficial effects of HRT and the lack of evidence suggesting a harmful effect on previously treated breast cancer, it is imperative that prospective trials be conducted to resolve the issue of the use HRT in these patients.

REFERENCES

1. Bush TL, Cowan LD, Barrett-Connor E, *et al.* Estrogen use and all-cause mortality: preliminary results from the Lipid Research Clinics Program Follow-Up Study. *JAMA* 1983; 249: 903-6.
2. Ettinger B, Genant HK, Cann CE. Long-term estrogen replacement therapy prevents bone loss and fractures. *Ann Intern Med* 1985; 102: 319-24.
3. Barrett-Connor E, Bush TL. Estrogen and coronary heart disease in woman. *JAMA* 1991; 265: 1861-7.
4. Nugent P, O'Connell TX. Breast cancer and pregnancy. *Arch Surg* 1985; 120: 1221-4.
5. Wile AG, DiSaia PJ. Hormones and breast cancer. *Am J Surg* 1989; 157: 438-42.
6. Spratt JS, Donegan WL, Greenberg RA. Epidemiology and etiology. In: Donegan WL, Spratt JS, editors. *Cancer of the breast*, 3rd ed. Philadelphia: WB Saunders, 1988: 56-8.
7. Turken S, Siris E, Seldin D, Flaster E, Hyman G, Lindsay R. Effects of tamoxifen on spinal bone density in women with breast cancer. *J Natl Cancer Inst* 1989; 81: 1086-8.
8. Love RR, Newcomb PA, Wiebe DA, *et al.* Lipid and lipoprotein effects of tamoxifen therapy in postmenopausal patients with node-negative breast cancer. *J Natl Cancer Inst* 1990; 82: 1327-32.
9. Sheth SP, Allegra JC. Endocrine therapy of breast cancer. In: Bland KI, Copeland EM III, editors. *The breast*. Philadelphia: WB Saunders, 1991: 939-40.
10. Bergkvist L, Adami HO, Persson I, Bergstrom R, Krusemo UB. Prognosis after breast cancer diagnosis in women exposed to estrogen and estrogen-progestogen replacement therapy. *Am J Epidemiol* 1989; 130: 221-8.