J. steroid Biochem. Vol. 23, No. 6B, pp. 1151–1154, 1985
Printed in Great Britain.

0022-4731/85 $3.00 + 0.00

ADJUVANT THERAPY FOR BREAST CANCER WITH POSITIVE AXILLARY NODES DESIGNED ACCORDING TO ESTROGEN RECEPTOR STATUS

SAUL E. RIVKIN*, WILLIAM A. KNIGHT III†, ROBERT MCDIVITT‡, TONY CRUZ¶, MARY FOULKES§, C. KENT OSBORNE**, CAROL J. FABIAN^A and JOHN J. COSTANZI^b

*Tumor Institute, Swedish Hospital, Seattle, Wash., †Medical Oncology Department, University of Texas, San Antonio, Tex., ‡Department of Pathology, Jewish Hospital of St Louis, 216 South Kings Highway, St Louis, Mo., ¶University of Texas, San Antonio, Tex., §Houston, Tex., **University of Texas Health Science Center, San Antonio, Tex., ^aMedical Oncology, University of Kansas, Kansas City, Kan. and ^bDepartment of Medical Oncology, University of Texas, Galveston, Tex., U.S.A.

Summary—This is a preliminary report of the Southwest Oncology Group—Adjuvant Therapy in Operative Breast Cancer with Positive Axillary Nodes—in which therapy is randomized by estrogen receptor (ER) data. ER− patients receive either 1 or 2 years of CMFVP. The ER+ group receive CMFVP for 1 year and/or hormonal therapy. ER+ patients have a significant longer disease-free interval compared to ER− patients ($P = 0.004$). There was no significant difference in disease-free interval for ER− patients who receive either 1 or 2 years of CMFVP. The data for ER+ patients is too preliminary to report for disease-free or total survival. Toxicity is acceptable because of frequent monitoring and examinations which results in the low percentage of life-threatening toxicity.

INTRODUCTION

This is a preliminary report of the Southwest Oncology Group Study No. 7827, in which hormonal receptor data dictates the type of adjuvant therapy for women with operable breast cancer and positive nodes. Estrogen receptor-positive (ER+) patients have a greater likelihood of responding to hormonal manipulations than ER− patients and the addition of endocrine therapy is being tested in this subgroup [1–4]. ER− patients have a higher risk for recurrence and poor survival. In this subgroup, 2 years of CMFVP chemotherapy is compared to the standard 1 year to test the hypothesis that more prolonged therapy may benefit this group.

The endocrine therapy chosen for premenopausal ER+ patients was surgical castration. This procedure was selected because of the potential for escape of premenopausal women treated with long-term antiestrogens and because other studies were testing the antiestrogen tamoxifen.

Tamoxifen was chosen as the endocrine therapy for postmenopausal ER+ patients because of its proven activity and lack of toxicity in such patients with advanced disease [5–10].

The chemotherapy chosen is "continuous" cyclophosphamide, methotrexate, 5-flourouracil, vincristine and prednisone (CMFVP). This regimen is given because it resulted in a prolonged disease-free survival in premenopausal and prolonged disease-free interval in postmenopausal patients with operable breast cancer with involved axillary nodes, when compared to melphalan [11, 12].

The basis for the design of this study was the ER content of the primary tumor. The objectives of this study are as follows:

(1) to compare the disease-free interval and overall survival in ER− patients (with operable breast cancer and positive axillary nodes), randomized to either 1 or 2 years of combination chemotherapy (CMFVP);
(2) to compare the disease-free interval and overall survival in ER+, premenopausal patients (with operable breast cancer and positive axillary nodes), randomized to either surgical oophorectomy and CMFVP for 1 year, or CMFVP for 1 year alone;
(3) to compare the disease-free interval and overall survival in ER+, postmenopausal patients (with operable breast cancer and positive axillary nodes), randomized to tamoxifen alone, CMFVP alone or tamoxifen + CMFVP for 1 year;
(4) to determine the effect of ER status on disease-free interval and survival.

EXPERIMENTAL

Selection of patients

All women who have had a modified or radical mastectomy with one or more positive axillary nodes and no evidence of metastatic disease upon histologic examination, are eligible for this study, provided they have fulfilled the specific criteria described in the

protocol. That criteria includes: primary and axillary neoplasm completely removed and confirmed by pathologic report, tumors confined to the breast and axilla, tumors moveable in relation to the underlying muscle and chest wall, axillary nodes moveable in relation to the chest wall and neurovascular bundle, no preoperative arm edema and leukocyte count $\geqslant 4000/mm^3$, platelet count $\geqslant 100{,}000/mm^3$ and blood urea nitrogen (BUN) $\leqslant 25$ mg%. Patients with inflammatory carcinoma or skin ulcerations >2 cm are excluded from this study. T_3 lesions (>5 cm dia are included if there is no fixation. Chemotherapy and hormonal therapy must be initiated within 42 days after mastectomy.

Patients who undergo segmental mastectomy and who receive postoperative radiation therapy as primary treatment are also eligible. Those patients electing a breast-sparing procedure may be treated with a lumpectomy and axillary dissection. This includes removal of the palpable mass with a small rim of normal breast tissue, but without performance of a quadrant resection. Following the lumpectomy, an axillary dissection including the lower and middle axillary nodes is completed. Patients selected for surgery for less than a total mastectomy, must have tumors limited to the breast or to the breast and adjacent lymph nodes upon clinical examinations. The primary breast lesions must be $\leqslant 5$ cm in the greatest diameter. Primary lessions may not be fixed to the overlying skin or to the underlying pectoralis muscle or fascia. Palpable axillary nodes must be mobile.

This study is being carried out on patients from 21 institutions affiliated with the Southwest Oncology Group. The patients are informed of the possible side effects and benefits of the treatment and sign consent forms.

Pretreatment study

All patients undergo the following studies: history and physical examination, bone scan, liver scan, mammogram, complete blood count, transaminase, alkaline phosphatase, bilirubin, BUN, serum creatinine, serum calcium, chest X-ray and ER (optional progesterone receptor) evaluation of the primary breast tumor. Brain scans are obtained if the patient has questionable symptoms and if laboratory tests suggested metastasis to those sites.

Experimental design

Stratification is done according to ER data, menopausal status, number of involved axillary nodes (1–3 and $\geqslant 4$), type of surgery and whether postoperative radiation is to be administered.

The treatment schema is as follows:

ER − → CMFVP for 1 year
ER − → CMFVP for 2 years

ER − women are randomized to receive combination chemotherapy for either 1 or 2 years, using the five-drug combination: cyclophosphamide, methotrexate, 5-flourouracil, vincristine and prednisone (CMFVP);

ER + premenopausal → CMFVP for 1 year
ER + premenopausal → CMFVP for 1 year + surgical oophorectomy

ER+ women, who are still menstruating, are randomized to receive CMFVP alone or CMFVP plus a surgical oophorectomy;

ER − postmenopausal → Tamoxifen for 1 year
ER − postmenopausal → CMFVP for 1 year
ER − postmenopausal → CMFVP + tamoxifen for 1 year

ER+ women, who are postmenopausal, are randomized to receive tamoxifen for 1 year, CMFVP for 1 year or a combination of CMFVP and tamoxifen for 1 year.

Combination chemotherapy doses are as follows:

5-flourouracil—400 mg/m^2 i.v. weekly for 1 or 2 years;

methotrexate—15 mg/m^2 i.v. weekly for 1 or 2 years;

vincristine—0.625 mg/m^2 i.v. weekly for 13 weeks, repeat on weeks 53–62 for *2nd year patients*;

cyclophosphamide—60 mg/m^2 p.o. daily for 1 or 2 years;

prednisone—30 mg/m^2 p.o. days 1–14, 20 mg/m^2 p.o. days 15–28, 10 mg/m^2 p.o. days 29–42, repeat starting day 366 for *2nd year patients*;

tamoxifen—10 mg p.o. b.i.d. for 1 year.

Surgical oophorectomy is performed within 6 weeks, following breast surgery.

Patients having undergone a breast-sparing procedure begin radiation therapy and chemotherapy no later than day 21. Radiation is given to the remaining breast tissue, chest wall and regional lymph node drainage area.

Radiation is also available to patients who have a primary mastectomy and axillary dissection. The

Table 1. Total eligible patients by treatment group

	Number
ER-patients	
CMFVP—1 year	194
CMFVP—2 years	197
ER+ premenopausal patients	
Combination chemotherapy (CMFVP)	60
Combination chemotherapy + surgical Oophorectomy	59
ER+ postmenopausal patients	
Tamoxifen (alone)	123
Combination chemo (CMFVP)	134
Combination chemo (CMFVP) + tamoxifen	127

dose schedule and radiation fields are not standardized. Most of the patients receive radiation to the anterior chest wall, supraclavicular, axillary and internal mammary nodes. When postoperative radiation is used, it is started 10 weeks after combination chemotherapy. (CMFVP).

Follow-up studies

While receiving chemotherapy patients receive a monthly physical examination and a weekly complete blood count. During the treatment period, transaminase, alkaline phosphatase, serum calcium and phosphorous, serum creatinine, BUN and urinalysis are obtained every 2 months. Bone scan and chest X-rays are taken every 6 months. At the completion of therapy, a physical examination, complete blood count, BUN, creatinine, alkaline phosphatase, calcium phosphatase, SGOT and bilirubin are repeated every 3 months. Chest X-rays are done every 6 months and a mammogram and bone scan is done every year.

RESULTS

At the time of this preliminary analysis, a total of 894 patients have been accrued on this adjuvant study (Table 1). Of the 894 patients, 59 patients are ineligible, 835 are eligible, 110 are too early to evaluate and 694 patients are fully or partially evaluable. The median follow-up time for all patients is 3.5 years.

Table 2. Recurrences in ER− patients, treated with either 1 or 2 years of CMFVP

	Recurrences CMFVP 1 year	CMFVP 2 years
	Number %	Number %
Total	36/157 = 23%	26/155 = 17%
Nodal status		
1–3	10/76 = 13%	8/74 = 11%
⩾4	26/81 = 32%	18/82 = 22%
	Premenopausal	
1–3	4/38 = 11%	3/36 = 8%
⩾4	11/43 = 26%	10/35 = 29%
	Postmenopausal	
1–3	6/38 = 16%	5/38 = 13%
⩾4	15/48 = 31%	8/47 = 17%

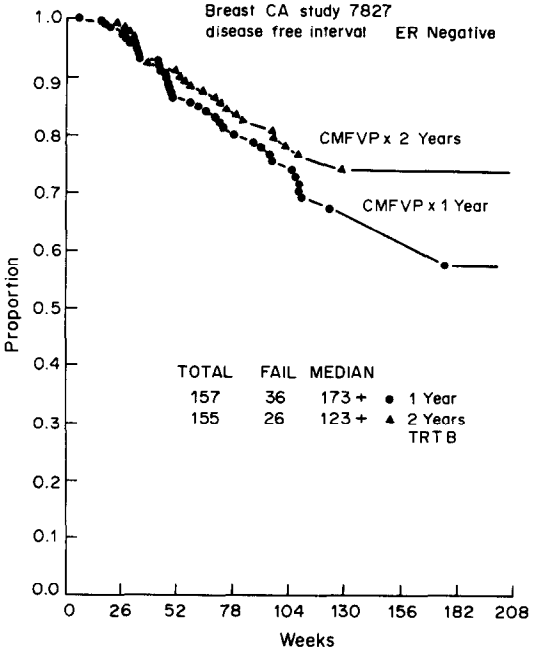

Fig. 1.

The data shown in the following tables and figures is based upon fully and partially evaluable patients.

Table 2 shows a preliminary analysis of the recurrence patterns for ER− patients. There is no statistical difference between 1 or 2 years of chemotherapy. Postmenopausal patients with ⩾4 positive nodes have had fewer relapses in the 2-year treatment groups. However, this is not statistically significant at the present time. Figure 1, shows a Kaplan–Meier estimation of the time to treatment failure (disease-free interval). There is no significant difference in treatment arms. ($P = 0.22$) It is too early at this time to present meaningful survival data. The prognostic value of ER status is observed in Table 3. The ER+ patients had fewer relapses in the 1–3 and ⩾4 nodal groups, when compared to ER− patients. Figure 2 shows a Kaplan–Meier plot comparing disease-free interval by ER status. This preliminary data reveals that ER− patients have an increased relapse rate as compared to the ER+ patients. This comparison has a two-tailed P-value of 0.004.

The data for ER+ patients is too preliminary to report for disease-free or total survival. Thus far, all treatment regimens have been well-tolerated. Leuko-

Table 3. Treatment failures according to ER status

	Recurrences ER−	ER+
	Number %	Number %
Total	62/312 = 20%	44/381 = 12%
Nodal status		
1–3	18/149 = 12%	10/179 = 6%
⩾4	44/163 = 27%	34/302 = 17%

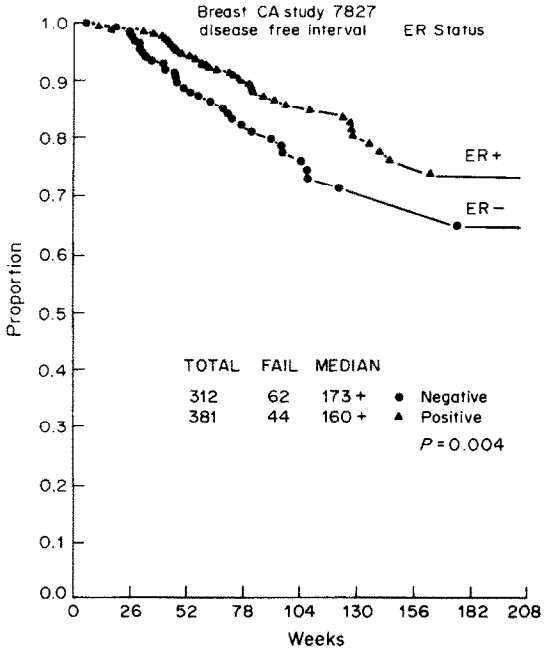

Fig. 2.

penia, gastrointestinal toxicity and neurotoxicity are the most frequent side effects and are mild to moderate. Only 4% of the patients developed some degree of hemorrhagic cystitis, secondary to cyclophosphamide. No toxic deaths have occurred and life-threatening toxicity has been rare, perhaps due to frequent physician monitoring. Life-threatening toxicity has occurred in only 1.7% of the patients. There have been no drug-related deaths.

Two patients who received tamoxifen had mesenteric-thrombosis; the relationship to tamoxifen is unclear.

DISCUSSION

This report is a preliminary analysis of an ongoing study and definite conclusions cannot be drawn. Preliminary findings are:

(1) in ER− patients, there appears to be no significant improvement in disease-free interval by prolonging the duration of CMFVP chemotherapy to 2 years;
(2) there is a higher relapse rate in ER− patients compared to ER+ patients; ($P = 0.004$).
(3) the most significant variable for disease-free interval is the number of axillary nodes.

Acknowledgement—This study was supported by Grant CA 20319-09.

REFERENCES

1. Knight W., Livingston R., Gregory E. and McGuire W.: Estrogen receptor: an independent prognostic factor for early recurrence in breast cancer. *Cancer Res.* **37** (1977) 4669.
2. Knight W., Livingston R., Gregory E. and McGuire W.: Absent estrogen receptor and decreased survival in human breast cancer. *Proc. AACR-ASCO* **19** (1978) 392.
3. McGuire W.: Current status of estrogen receptor in human breast cancer. *Cancer* **36** (1975) 638–644.
4. McGuire W. *et al.*: Current status of estrogen and progesterone receptors in breast cancer. *Cancer* **39** (1977) 2932–2937.
5. *Investigational Drug Brochure for ICI 46, 474,* Clinical Research Department, United States Inc., Wilmington, 19897.
6. Lerner H. *et al.*: Phase II study of tamoxifen: report of 74 patients with stage IV breast cancer. *Cancer Treat. Rep.* **60** (1976) 1431–1435.
7. Manni A. *et al.*: Antiestrogen-induced remissions in stage IV breast cancer. *Cancer Treat. Rep.* **60** (1976) 1145–1450.
8. Morgan L. *et al.*: Therapeutic use of tamoxifen in advanced breast cancer: correlation with biochemical parameters. *Cancer Treat. Rep.* **60** (1976) 1437–1443.
9. Moseson D. *et al.*: Antiestrogen therapy of advanced human breast cancer. Unpublished data.
10. Tormey D. *et al.*: Evaluation of tamoxifen dose in advanced breast cancer: a progress report. *Cancer Treat. Rep.* **60** (1976) 1451–1459.
11. Glucksberg H. *et al.*: Combination chemotherapy (CMFVP) vs L-PAM for operable breast cancer with positive axillary nodes. *Cancer Treat. Rep.* **50** (1982) 423–434.
12. Rivkin S. *et al.*: *Current Controversies in Breast Cancer.* Univ. of Texas Press, Austin, Tex. (1984) pp. 501–510.