J. steroid Biochem. Vol. 23, No. 6B, pp. 1155–1160, 1985
Printed in Great Britain.

0022-4731/85 $3.00 + 0.00

ADJUVANT TREATMENT IN OPERABLE BREAST CANCER

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Summary—The object of Ludwig III was to assess adjuvant therapy after total mastectomy and axillary clearance in postmenopausal women with breast cancer and axillary node metastases. Chemo-endocrine therapy (cyclophosphamide, methotrexate, 5-fluorouracil, prednisone and tamoxifen: CMFp + T) was compared with endocrine therapy (prednisone and tamoxifen: p + T) and with no adjuvant treatment in 463 evaluable patients aged 65 years or less. Treatment results are available (Ludwig Breast Cancer Study Group, *Lancet* i (1984) 1256–1260). Nodal status and receptor content of the primary were found to have prognostic value, while tumor size did not.

INTRODUCTION

Clinical trials of postoperative adjuvant drug treatment in operable breast cancer have demonstrated that chemotherapy and hormonotherapy, separately or combined, may significantly increase the disease-free survival [1–5]. Recently, adjuvant endocrine therapy has been shown to delay recurrence and to prolong survival [6–8], and a combination of chemotherapy and endocrine therapy has increased the relapse-free survival in patients 50 or more years of age when compared to chemotherapy alone [9]. In 1978 the Ludwig Breast Cancer Study (LBCS) Group (participating clinics in Appendix 1) initiated four complimentary randomized controlled clinical trials to evaluate adjuvant therapy in both pre- and postmenopausal patients with operable breast cancer and axillary lymph node involvement (Table 1). Antiestrogens in combination with chemotherapy were used in the younger postmenopausal patients (Ludwig III), and that trial is the subject of this report.

EXPERIMENTAL

From July 1, 1978, to August 31, 1981, the participating institutions of the LBCS Group (Appendix 1) entered 503 patients into LBCS III. This analysis was made on data available as of May 1, 1983, with a median follow-up of 31 months.

Table 1

	Surgery	*Randomize*
I	Pre- and Perimenopausal 1–3 N(+)	CMF CMFp
II	Pre- and perimenopausal 4 or more N(+)	CMFp Oophorectomy + CMFp
III	Post-menopausal all N(+), 65 years or less	Observation CMFp + TAM p + TAM
IV	Post-menopausal all N(+), 66 years up to 80 years	Observation p + TAM

C: Cyclophosphamide 100 mg/m² p.o. on Days 1 through 14 of each cycle.
M: Methotrexate 40 mg/m² i.v. on Days 1 and 8 of each cycle.
F: 5-fluorouracil 600 mg/m² i.v. on Days 1 and 8 of each cycle.
p: Prednisone 7.5 mg/day p.o.
TAM: Tamoxifen 20 mg p.o. daily.

Eligibility and patient entry

Postmenopausal women, defined by menstrual history or by endocrine testing (Table 2), who were 65 years of age or less and who had histologically confirmed breast cancer with axillary lymph node metastasis were considered for eligibility. Treatment by total mastectomy and axillary clearance for disease staged according to the International TNM Classification as $T_{1A \text{ or } B}$, $T_{2A \text{ or } B}$, T_{3A}, $N_{0 \text{ or } 1}$ (but with histologically-proven axillary node metastasis), M_0 was a requirement. A chest radiograph and bone scan (with X-rays of "hot spots", if applicable) were required for exclusion of detectable metastatic disease. A peripheral white blood cell count of $\geq 4000/mm^3$, a platelet count of $\geq 100{,}000/mm^3$, creatinine of $< 130\ \mu mol/l$, bilirubin $< 20\ \mu mol/l$ and SGOT of < 60 IU/l were also required. Patients who were bedridden or who were not fit for any of the therapeutic options (including follow-up) were ineligible. Additional ineligibility criteria included: breast tumor other than carcinoma; inflammatory cancer; bilateral breast cancer; other prior or concurrent malignancy; and previous therapy for any cancer (except basal and squamous carcinomas of the skin or cervical carcinoma *in situ*). Patient entry and evaluability are reported in Table 3. Table 4 summarizes the distribution of relevant patient characteristics for each therapy. The treatment groups were generally well balanced for known prognostic factors recorded at entry.

Surgical technique

The protocol required that all patients have at least a total mastectomy with axillary clearance. Removal of the pectoral muscles was optional but recorded.

Randomization and Stratification

All patients were randomized by telephone or telex through the Study Coordination Center in Bern,

Table 2. Definition of postmenopausal patients

	Condition	Age restriction to be considered postmenopausal
A.	At least 1 year amenorrhea and uterus intact	Older than 52 years
B.	At least 3 years amenorrhea and uterus intact	52 years or younger
C.	Biochemical evidence of cessation of ovarian function for doubtful patients with regard to A. and B.	Any age
D.	Hysterectomy without bilateral oophorectomy	56 years or older
E.	More than 1 year after bilateral oophorectomy	Any age

Switzerland. The randomization was stratified by participating clinic (see Appendix 1). The randomization schedule was produced using pseudo-random numbers generated by a congruence method executed on a DEC-2060 computer.

Adjuvant treatment regimens

Details of the treatment regimens are given in Table 1. Treatment started within 6 weeks of surgery and continued through twelve 28-day cycles of chemo-endocrine therapy or 12 months of endocrine therapy alone.

Doses were modified as follows: full dosage of CMF was administered to patients with WBC $\geq$ 4000/mm^3 and platelet count $\geq$100,000/mm^3. Fifty percent dose was given to those with WBC 2500–3999/mm^3 and/or platelet count $\geq$50,000/mm^3 but below 100,000/mm^3. CMF was not administered if blood counts were below these levels. Criteria were also established for prospective dosage modification due to extreme hematologic toxicity, muscositis and cystitis.

Receptor determination

Participants were urged to remove tumor tissue for receptor analysis at the time of surgery. The participating laboratories adopted standardized methods for estrogen and progesterone receptor assays following individual laboratory assessment of standards provided by the coordinating laboratory. Estrogen receptor results of $\geq$10 fmol/mg cytosol protein were classified as positive and values below this were classified as negative. ER results were available for 51% of the patients.

Pathology

Tumor size and lymph node status were determined by the clinic pathologist. Tumor type, grade, necrosis, and other histological aspects of tumor and host tissue relationship were determined by central pathology review which was achieved in 96% of the patients.

Follow-up

Clinical assessment was required every 3 months for 2 years and every 6 months thereafter until death. White blood cell and platelet counts, serum calcium and creatinine, and liver function tests were required with each clinical follow-up. Chest X-rays and bone scans were required every 6 months. After 2 years a bone scan was required once yearly.

Relapse

Acceptable evidence of relapse was provided by histological or cytological means or by a clear progression of disease as assessed by indirect methods such as radiological or isotopic studies. The time of relapse was defined as the time when recurrent disease was confirmed or was suspected and later confirmed.

STATISTICAL METHODS

The study objective of 150 evaluable patients per treatment was reached after three years of entry. Failure was defined as any recurrence, appearance of second primary malignancy, or death, whichever occurred first. All study records (on-study, treatment, toxicity and recurrence) were reviewed centrally by

Table 3. Patient entry and evaluability by study and treatment assignment

	CMFp + T	p + T	Obs.	Total
LBCS III				
Patients entered	171	164	168	503
Noncompliant clinic*	4	3	3	10
Refused follow-up†	3	2	0	5
Ineligible‡	10	6	9	25
Cases evaluable	154 (90%)	153 (93%)	156 (92%)	463 (92%)

*One institution was dropped from participation because patients entered on study were either ineligible or had major deviations from protocol therapy. The decision to drop the institution was made in November, 1981.

†Insufficient data were available for 5 patients who refused treatment assignment and follow-up.

‡Ineligible patients were not included in the analyses reported.

Reasons ineligible: 5 cases—primary more than T_{3A}, or metastic disease. 8 cases—randomized to wrong study based on menopausal status or age. 5 cases—previous or concurrent malignancy. 7 cases—other.

Table 4. Patient characteristics in percent (evaluable patients only)

	LBCS III: Postmenopausal patients 65 years or younger			
	CMFp + T	p + T	obs.	Total
No. of patients	154	153	156	463
median age	60	59	59	59
(range)	(46–65)	(45–65)	(40–65)	(40–65)
Nodal status				
N+ 1–3	58%	54%	55%	56%
N+ ≥4	42%	46%	45%	44%
ER Status				
ER+	38%	29%	34%	33%
ER−	12%	20%	21%	18%
ER unknown	50%	51%	45%	49%
Tumor size in cm (pathology)				
≤2 (T_1)	36%	39%	30%	35%
2,1–5 (T_2)	57%	57%	62%	59%
>5 (T_3)	7%	4%	8%	6%
Surgical procedure				
radical or modified radical mastectomy	36%	41%	39%	38%
total mastectomy + axillary clearance	64%	59%	61%	62%
Central pathology review (for 96% patients)				
Histological type				
infiltrating ductal ca	66%	67%	63%	65%
others	34%	33%	37%	35%
Pathological grade				
1	26%	19%	19%	21%
2	44%	48%	53%	48%
3	30%	33%	28%	31%

the study coordinator. In addition, there was central data management review of all records during the course of the study. The Kaplan–Meier method [10] was used to estimate survival distributions. The log-rank procedure [11] was utilized to assess the statistical significance of treatment differences between these survival distributions. Times were measured from the data of randomization. All eligible patients with follow-up data were included.

Policy

Because of the decision of the LBCS Group not to publish treatment results until a major report has been accepted for publication, this report will be limited to the evaluation of prognostic factors, of toxicity, and of dose–response effect of chemotherapy (September, 1983).

RESULTS

All patients in Ludwig III were divided into groups of known prognostic factors.

Nodal status

Eighty-three of 258 patients with 1–3 lymph nodes involved (32.5%) relapsed as compared to 106 of 205 (52%) of patients with 4 or more positive lymph nodes ($P = 0.0001$). The death rates in these patient groups were 16% (41/258) and 25% (51/205), respectively ($P = 0.026$).

Receptor status

Fifty-three of 156 patients with ER-positive tumors (34%) relapsed as compared to 44 of 82 patients with ER content lower than 10 fmol/mg cytosol protein [53%] ($P = 0.004$). The death rates were 11% (13/156) and 35% (44/82), respectively ($P = <0.0001$).

Tumor size

Fifty of 162 patients with a T_1 tumor (31%) failed as compared to 139 of 301 patients with a primary tumor stage of more than T_1 (46%). The difference is statistically significant ($P = 0.0008$). Twenty-two patients with T_1 tumors died as compared to 70 patients with a primary tumor staged as more than T_1 [14 vs 23%] ($P = 0.013$). The surgical procedure (radical or modified radical mastectomy vs total mastectomy, without partial or total removal of one of the pectoralis muscles) was found not to have any influence on disease-free survival ($P = 0.22$) or survival ($P = 0.86$).

Toxicity

Hematologic and other toxicities are listed in Table 5. The incidence of severe hematologic and non-hematologic toxicity (excluding alopecia) in patients who received CMFp + T (22%) was higher than the same grade of complications observed in patients who had p + T alone [3%] ($P = 0.0001$). No fatalities were definitely attributable to treatment, but as shown in Table 6, 11 patients died without evidence of recurrent disease (6 of them during or immediately after therapy).

Compliance

Major deviations from the protocol therapy occurred in 26 patients (5.6%). Sixteen patients assigned to CMFp + T received less than 6 cycles (3 patients received none) because of refusal. Six patients who were assigned p + T had major protocol

Table 5. Incidence of toxicity by treatment regimen

	LBCS III CMFp + T		LBCS III p + T	
	Mild/mod	Severe	Mild/mod	Severe
Leukopenia*	76%	4%	6%	—
Thrombocytopenia*	40%	7%	3%	—
Nausea, vomiting, xerostomia, anorexia, epigastric pain	77%	9%	10%	1%
Diarrhea	19%	0.7%	1%	—
Stomatitis; mucositis	28%	4%	—	—
Conjunctivitis, keratitis	13%	1%	0.7%	—
Skin toxicity (rash)	3%	0.7%	5%	—
Alopecia (complete/incomplete)	26%/43%	—	—	—
Hepatotoxicity	1%	—	—	—
Cystitis	18%	0.7%	—	—
Thrombosis, thrombophlebitis, embolism	6%	4%	3%	0.7%
Cushingoid, weight gain, edema	21%	0.7%	17%	0.7%
Hot flashes, vaginal bleeding	9%	0.7%	9%	—
Hyperglycemia	—	—	4%	—
Neurologic, depression, euphoria, etc.	10%	3%	5%	—
Infection	15%	0.7%	3%	—
Hemorrhage	3%	—	—	0.7%
Reported worst degree	70%	22%	43%	3%

Mod = Moderate.
*Mild/Moderate: WBC 3999–1000/mm^3; plates 99,999–50,000/mm^3.
Severe: WBC $<1000/mm^3$; platelets $<50,000/mm^3$.

Table 6. Incidence of mortality without evidence of cancer in different treatments

	LBCS III Age 65 or younger		
	CMFp + T	p + T	obs.%
Cardiovascular disease	5(4)	3(1)	0
Peritonitis (perforated ulcer)	1(1)	0	0
Other	1	0	1

Events in parentheses occurred on treatment within the first year.

deviations: 3 refused all p + T, 2 received therapy for 3 months or less, and 1 received CMFp + T. Four patients in the observation group were given additional treatment (tamoxifen and/or radiation) for breast cancer without evidence of relapse. Objective and subjective toxicity was the main cause for dose reduction, especially with CMFp + T treatment. Analyses of treatment outcome by dose administered were performed for 3 dose levels [12]. Differences in disease-free survival between the 3 dose levels were not statistically significant ($P = 0.82$; Fig. 1). The average CMF dose delivered in Cycles 1–6 was significantly higher than the average CMF dose given in Cycles 7–12. 53% of the patients received at least 80% of the full dose over the first 6 cycles while only 25% of the patients received at least this average dose in the last 6 cycles ($P = 0.0001$). Fifteen patients who failed within the first year were excluded from this analysis. Evaluation of the effect of CMF dose reduction in Cycles 1–6 on disease-free survival revealed no difference between the group which received complete doses and the groups in which doses were reduced

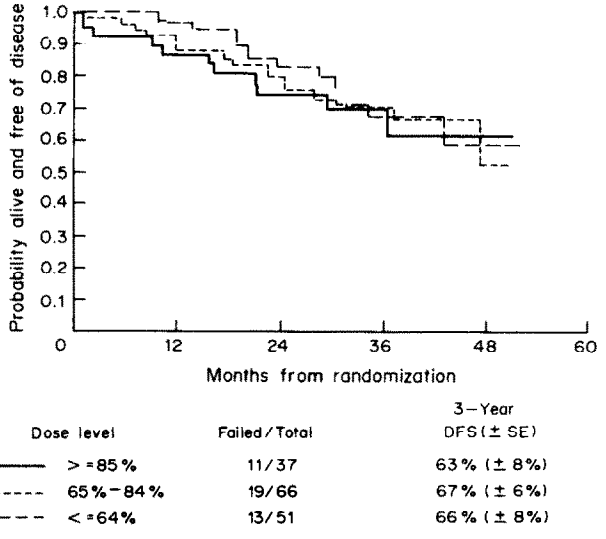

Fig. 1. Disease-free survival by CMF dose level received (LBCS III: CMFp + T treatment group).

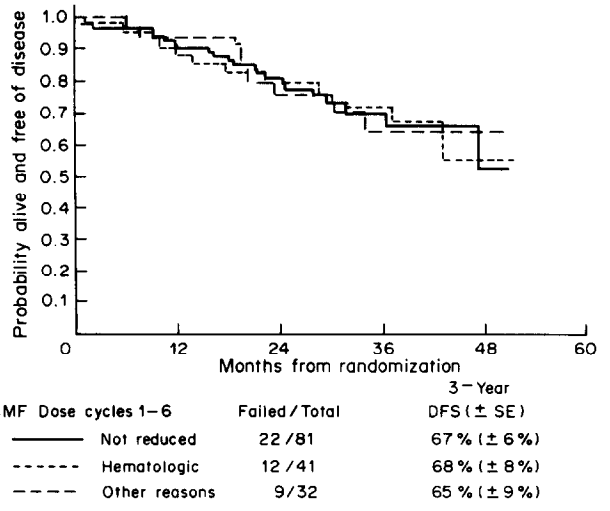

Fig. 2. Disease-free survival by CMF dose received in cycles 1–6 (LBCS III: CMFp + T treatment group). No dose reduction (≥80% dose received) *versus* dose reduction mainly due to hematologic toxicity *vs* dose reduction mainly due to other reasons.

because of hematologic toxicity, or for other reasons ($P = 0.99$; Fig. 2).

The analysis of CMF dose and therapeutic effect in the CMFp + T-treated patients failed to reveal a difference in disease-free survival among the patients receiving the three different dose levels, in contrast to retrospective results obtained by other groups. This could be due either to an absence of a dose–response effect within the dose ranges administered or to a complex interaction between the chemotherapy and endocrine therapy which reduces the potential positive effects of higher doses.

CONCLUSIONS

Four hundred and sixty three evaluable young postmenopausal patients (under the age of 66 years of age) were accrued in 3 treatment groups: chemo- and endocrine therapy, endocrine therapy alone, and no further treatment after mastectomy. The decoded treatment results have been presented elsewhere. Central pathology review is available on 96% of the patients.

Estrogen receptor assay results from quality controlled laboratories are available for 51% of the patients. An undefined interaction between the chemotherapy and endocrine therapy might be responsible for the apparent lack of a dose–response relationship in patients who received CMF.

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APPENDIX 1

LUDWIG BREAST CANCER STUDY GROUP

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