Adjuvant ovarian ablation versus CMF chemotherapy in premenopausal women with pathological Stage II breast carcinoma : the Scottish trial.

Scottish Cancer Trials Breast Group and ICRF Breast Unit, Guy's Hospital, London

Background

Breast cancer is both a common (27.6% of female cancers, 2831 cases in NSW in 1991) and fatal (18.8% of female deaths from cancer, 900 deaths in NSW in 1991) condition(49). The disease is frequently the subject of papers. Unfortunately many are retrospective analyses that at best indicate promising therapies. Randomised trials in breast cancer are increasing in number. Only 2-3% of women with breast cancer are included on randomised trials and some commentators have suggested increased recruitment would more quickly resolve and optimise management issues, especially since such trials require at least 10 years follow-up to provide solid data on toxicity, survival and effect(65).

Within the setting of operable breast cancer (i.e., Stage I and II) randomised trials have addressed the usefulness of post-lumpectomy radiotherapy(39), chemotherapy(56,57,58), and hormone therapy(59). The Scottish Cancer Trials Breast Group (SCTBG), like the NSABP and other joint groups, have embarked on a series of trials that stratify patients on the basis of known prognostic factors. The introduction describes the institution of two trials in 1980 involving post-operative patients. The first trial examined the effect of tamoxifen in non-premenopausal women and reported an improved survival(59).

The second trial, which is described in this report, collected the premenopausal, node-positive group in an attempt to quantify the effects of chemotherapy (CMF) and ovarian ablation (OA) in a randomised trial. Although the possible confounder of chemotherapy-induced ovarian ablation was recognised at trial inception, no controlling attempts were made.

Summary

The SCTBG report a multi-institutional, randomised clinical trial comparing, in post-operative Stage II breast cancer patients with positive nodes, the adjuvant use of ovarian ablation or CMF chemotherapy, and the use of prednisolone.The trial accrued 332 patients between March, 1980 and May, 1990. The study found no significant differences in the effect of ovarian ablation or CMF chemotherapy, or prednisolone use after a median follow-up of 5.9 years.

Trial Design

Hypothesis

The proposed null hypothesis is not stated.

Sample size and Statistical Power

This study does estimate power. Although not referenced, they have estimated possible differences that they could detect with 100 events. Also they estimate an 80% power of detecting a 15% difference.

Using Casagrande's method(29), a trial with 160 patients in each arm (OA v CMF, Pred+ v Pred-) with a 50% 10-year survival rate would indeed give an 80% power of detecting a 15% difference, and a 90% power of detecting a 20% difference (two-tailed). Similar sample sizes are required for the 60% 5-year survival calculation.

The authors gave no estimate of the pre-trial likelihood of difference. This trial would have benefited from the inclusion of at least 400 patients in each arm, thus permitting a 10% difference to be confidently sought.

Trial Conduct

Eligible Population

The eligible patients were premenopausal women with operable breast cancer that involved a single invasive cancer and non-fixed histologically positive axillary nodes. They had no evidence of metastatic disease on routine assessment by chest and pelvic radiology, and blood tests as clinically indicated. Some evidence of axillary status (at least axillary node sampling) was required for entry.

Patient Selection

Selection criteria applied are poor.

The numbers of potential cases available during the study period was not determined. While all surgeons were involved for at least 4 years, and the Scottish contingent for 10 years, the 43 surgeons entered only 332 patients over

10 years. This small number indicates that, given that the method of enrolment until 1985 was the surgeon's discretion, an unquantitated selection bias was operating.

The trial purports to examine a therapeutic option in Stage II breast cancer by selecting patients with T0-3 N0-2 disease. However, the 1978 AJC classification grouped T1N1, T2N0, T2N1 disease together in Stage II, with T3 or N2 disease classified as Stage IIIa. Stage I included T1N0 disease only. Thus the selected group probably includes a range of patients Stage I-III. The table describing patients should include this data.

Patient Stratification

Estrogen receptor (ER) status was not used for stratification, only region (Scotland I-III, Guy's Hospital) and extent of axillary surgery (sampling/Level I dissection v clearance).

Patient Randomization

Randomization occurred after stratification by random number assignment to one of four treatment arms (Table 1). This method is acceptable.Table 1: Treatment groups into which patients were assigned

I	Ovarian Ablation	Prednisolone
II	Ovarian Ablation	
III	CMF chemotherapy	Prednisolone
IV	CMF chemotherapy	

Patient Exclusion

No patient exclusions occurred after randomization. The Trials Office verbally checked eligibility criteria before randomization. Ineligible candidates were therefore not randomised. No details are given concerning the number of patients who failed on eligibility criteria after a call was placed, nor whether patients could be re-presented for evaluation at a later date.

The report title described the population as "Stage II" breast cancer, however there are no indications of criteria applied to separate patients with Stage I/III disease.

Patients were excluded if "... mentally or physically unsuitable for entry". Such a general criteria, which could mean a psychiatric diagnosis or a personality disorder not looked on favourably by the enrolling surgeon, introduces a selection bias, severely compromising the external validity of the study. The other exclusion criteria were reasonable.

Treatment Description

*Surgery*The extent of surgery varied throughout the trial period.

- the breast was initially treated with mastectomy. After 1984, surgeons were permitted to undertake a lumpectomy with post-operative radiotherapy to the breast. Published data from this era(60) indicate that the difference in management would not be expected to affect results, and are confirmed with longer follow-up(39).
  The group of mastectomy patients who did not undergo complete axillary clearance received radiotherapy to the nodal areas and to the chest wall. Nodal irradiation would be expected to achieve comparable control(61). Chest wall irradiation, however, would reduce the rate of local recurrence in the post-mastectomy high risk group(62), thus placing the mastectomy plus complete clearance group at higher risk of local relapse(63). Lack of specific figures prevent quantification of this effect.
- the axilla was inconsistently treated with either nodal sampling or formal Level I-III dissection. Less than a Level III dissection was classed as a nodal sampling procedure. The application of radiotherapy to the nodal sampling group is likely to achieve the equivalent control rates to nodal clearance(61), and possibly increased side effects.

There is insufficient information provided to permit the reader to determine indications for differing nodal treatments.

Radiotherapy

Radiotherapy was applied in two circumstances.

- radiotherapy after less than axillary clearance. The radiotherapy fields employed covered the chest wall and draining lymphatics at risk (presumably supraclavicular fossa and axillary fields).
- radiotherapy after less than mastectomy. The radiotherapy fields covered only the breast. A boost field was recommended.

Insufficient data was presented to permit estimation of total dose, dose-fractionation schedules, beam energy or field

orientation.

Ovarian ablation

Surgical or radiation ablation was undertaken. The reasons for selecting either modality were not addressed, nor were the success rates after each treatment.
The time limit for surgical ablation was 3 months, however it is unclear whether this was the protocol-determined period, or the maximum delay in achieving the ablation by this method.
Radiation ablation had no time limit, and was achieved by 15Gy in 5 fractions (megavoltage) or 12.5Gy in 5 fractions (orthovoltage) using parallel opposed fields. Women with large separations would have received more dose heterogeneity with orthovoltage treatment. This dose would induce menopause in most women, but not necessarily in younger women (<30)(64). Unless radiation ablation was confined to older premenopausal women, a potential confounder is introduced.

Chemotherapy and Drug therapy

The regime used for chemotherapy was well described with respect to dose, route of administration, frequency and dose modification.
The chemotherapy regime was also varied during the course of the trial. A reduction from eight 3-weekly cycles to six 3-weekly cycles occurred in December 1984. The reasons for this change are not delineated, but data from Milan suggests that the two regimes would be equally effective(58).
Within the group randomised to chemotherapy, 145 were treated, 6 received ovarian ablation, 3 received tamoxifen and 11 had no treatment. The planned delivery of chemotherapy was satisfactorily achieved.
The ovarian ablation and chemotherapy commencement times was not included in the protocol. The mean delay after surgery was 4 weeks (1-23) for chemotherapy and 6 weeks (0-22) for ovarian ablation. In addition to this heterogeneity of institution of therapy, there was variation in the temporal sequencing of chemotherapy and radiotherapy.

Table 2	Sequence of radiotherapy and chemotherapy
concurrent	61%
preradiotherapy	6%
postradiotherapy	32%
sandwich technique	23%

Prednisolone therapy is adequately described.

Pathology

No central review of the pathological diagnoses was undertaken.

Trial Analysis
Statistical Analysis

The authors analysed their results using Kaplan-Meier survival plots. Rather than using the conventional log-rank method for comparing the populations, the authors used a hazard ratio calculation, allowing the inclusion of specific variables within the setting of varying periods of follow-up.
An intention-to-treat analysis was employed(30). In the setting of a trial where two treatments may be nearly equivalent, the use of the intention-to-treat principle can mask a difference since the magnitude of any absolute advantage will be diminished by the inclusion of patients not receiving the advantageous treatment. In this case, a further analysis of treatment received should have been undertaken to enhance the robustness of their conclusions.
A subset analysis of receptor status utilised the same statistical methods, including treatment-given and intention-to-treat analysis. Interestingly, levels of 5 fmol/mg were used to designate receptor status, but a 20 fmol/mg cut-off was used in this analysis. A sensitivity analysis using alternative arbitrary cut-off points revealed the same results at 10 fmol/mg.The effect of pathology laboratory performance on end point analysis revealed no significant differences.

Confounding Variables

1. consent obtained versus no consent
Until 1985, surgeons entered 'suitable' cases without patient consent. Although no longer ethically acceptable, such an enrolment strategy is statistically acceptable if all eligible patients are entered without selection. The low numbers of patients entered indicates substantial pre-randomization selection by the surgeons. After 1985, patients were asked for their consent to be entered. This strategy will necessarily enrol a different population. Rates of consent were not described. The group is therefore heterogeneous with respect to selection. The two patient groups' characteristics and results are not compared to quantify the effect of surgeon or patient selection.

2. CMF chemotherapy for eight cycles versus CMF chemotherapy for six cycles
3. Mastectomy versus Lumpectomy and breast radiotherapy
4. Axillary clearance versus Axillary dissection/sampling and nodal radiotherapy
   As discussed previously, these alterations would be expected to have little effect on mortality or local relapse rates.
5. postmastectomy chest wall irradiation in high-risk patients determined by axillary surgery.
   The patients identified whose axillary clearance revealed a high risk of chest wall recurrence received no chest wall irradiation. Those who underwent lesser axillary manipulation received chest wall irradiation. The similar rates of nodal clearance in each group do not indicate an even distribution of this variable.
6. the success of radiation ablation
   An ablative dose of 15Gy/5Fx (MV) in women aged 26 to 57 will have variable success. The lack of success of radiation ablation in younger women could bias the results of ovarian ablation.
7. the effect of chemotherapy-induced menopause
   This confounding variable was recognised as a controversial issue at the trial's inception, nonetheless, attempts to control for its influence were not instituted and data collection concerning menopause was poor. The authors have not attempted subset analysis of the CMF chemotherapy groups with respect to menopause induction to ascertain the likelihood of this confounder operating. The analysis of receptor status is not an adequate surrogate for this question.
8. possible inclusion of breast cancer stages other than Stage II
9. the sequencing of chemotherapy and radiotherapy was variable

Trial Outcome
Criteria for Evaluation

Endpoints

Clinically relevant endpoints were recorded and were well defined.
Histologically proven non-invasive disease (e.g., DCIS) was defined as a new primary cancer. The classification of such an ipsilateral lesion was not clear.
The analysis utilised "event-free survival" and overall survival. The surrogate end-point, event-free survival, could be deleted since it includes only one contralateral event. The important endpoints are breast cancer recurrence and mortality.Receptor status determination at the three centres lacked quality control, especially in the earlier part of the trial. Interlaboratory variations should have been settled before the trial commenced. A measure of variability should be provided in this publication since the article referenced is difficult to obtain.

Bias

The lack of definition of the "Stage II" patient and the selection bias of the surgeon (unstated inclusion and mental status exclusion criteria) are the major biases. These factors diminish the external validity of the trial.
The arbitrary definition of receptor positivity at the 5fmol/mg level does not correlate with clinical experience. The selection of the clinically relevant level (20 fmol/mg) would be more reasonable with a later sensitivity analysis looking for additional effect in the levels less than those clinically relevant.

Toxicity

There are no reports of prednisolone or radiotherapy toxicities, or of deaths due to treatment. Prednisolone did not ameliorate chemotherapy-induced changes in haematological system, or mucosal tissues. Moderate-severe toxicity was common (Table II).
Menopause induced by chemotherapy was common especially in the over 40 years group (70% v 15%). With relapse and death rates equivalent between the OA and CMF groups, and such a high rate of menopause induction by CMF, it is difficult to determine the mechanism of CMF action, i.e., by cytotoxic action or hormonal effects ("chemical ovarian ablation"). No analysis was undertaken to address this confounding variable. The non-stratified subset analysis of receptor positivity does not address this question directly.

Loss to follow-up

No losses are described.

Protocol Violations

The authors do not report any inappropriate inclusions.
The incorrect therapy was given to 13% of patients. Within the systemic therapy randomization, 8 patients received the wrong treatment (CMFx2, OAx6), 6 received additional treatment (tamoxifen), and 30 received less treatment (no systemic therapy in 22, no radiotherapy in 8). Only 7 violations involved prednisolone treatment. This level of violation borders on the excessive, and should be kept to a minimum especially in circumstances where therapy differences may be small.

Results

The analysis showed that :
1. the addition of prednisolone to OA or CMF does not result in improvement in survival (overall or event-free).
2. in the premenopausal setting, the magnitude of therapeutic improvement derived from OA is not different to that of CMF.
3. the CMF regime (cyclophosphamide 750mg/m2, methotrexate 50 mg/m2, 5-fluorouracil 600mg/m2 by IV bolus every 3 weeks for 6-8 cycles) is safe and likely to produce menopause in patients with regular menses (67% overall).
4. with respect to estrogen receptor (ER) content :

   a. patients with high ER content tumours (>20 fmol/mg) have a better survival when treated with OA.
   b. patients with low ER content tumours (<20 fmol/mg) have a better survival when treated with CMF.

5. with respect to treatment assigned :

   a. following CMF treatment, patients with low ER tumours had marginally better survival than patients with high ER tumours.
   b. following OA treatment, patients with high ER tumours had much better survival than patients with low ER tumours.

Conclusion

The authors conclude that the outcome for ovarian ablation is very similar to that of CMF chemotherapy, certainly less than a 15% difference on these patient numbers. Prednisolone has no additional advantage to either of the above treatments and does not ameliorate CMF toxicity.They state that this trial provides evidence that the estrogen receptor status may impinge on the choice of adjuvant therapy, that the degree of effect is clinically significant and call for further attempts to quantified its magnitude.They point to other data that suggests that CMF chemotherapeutic benefits results from both hormonal and cytotoxic effects.

OVERVIEW

On first reading this seemed like a 'reasonable' trial, but on closer inspection, has been found wanting in several facets :

a. internal validity_The trial lacks sufficient numbers to detect a small difference between the treatments. The trial is confounded by the suboptimal use of radiation ablation, and the alteration in selection procedures, chemotherapy and surgery during the trial._

b. external validity_The presence of changing, inadequate and unnecessary selection criteria (consent, stage, mental/physical ability respectively) indicate that this is a heterogenous group selected from an unknown available pool. I could not match these patients with those derived from our clinics. The description of radiotherapy given has inadequate detail.The effect of receptor status in predicting response to CMF or OA in premenopausal patients is worthy of further study with a randomised trial of CMF and OA in different receptor states._

c. advancement of medical knowledge_The recognition of the fundamental confounder, CMF ablation, should have prompted a trial design with the ability to detect both the individual effects of CMF and OA, but also attempt to control for the menopause inducing effects of CMF. Such a trial would require many patients. One possible design might randomly apply OA in patients post-CMF after stratification for resultant menopausal status._

The trial provides a sign post for further study but, by itself does not add to or clarify treatment decisions for Stage II breast cancer patients. The conclusions of the authors are not supported because of trial deficiencies.