



**ANGLO CELTIC COOPERATIVE ONCOLOGY GROUP
CLINICAL TRIAL PROTOCOL**

“OPTION”

ANGLO CELTIC V

Trial Administration by: ISD CANCER CLINICAL TRIALS TEAM

Study No: BR0402

ISRCTN84856516

Study Title: **Ovarian Protection Trial In Oestrogen Non-responsive Premenopausal Breast Cancer Patients Receiving Adjuvant or Neo-adjuvant Chemotherapy “OPTION”**

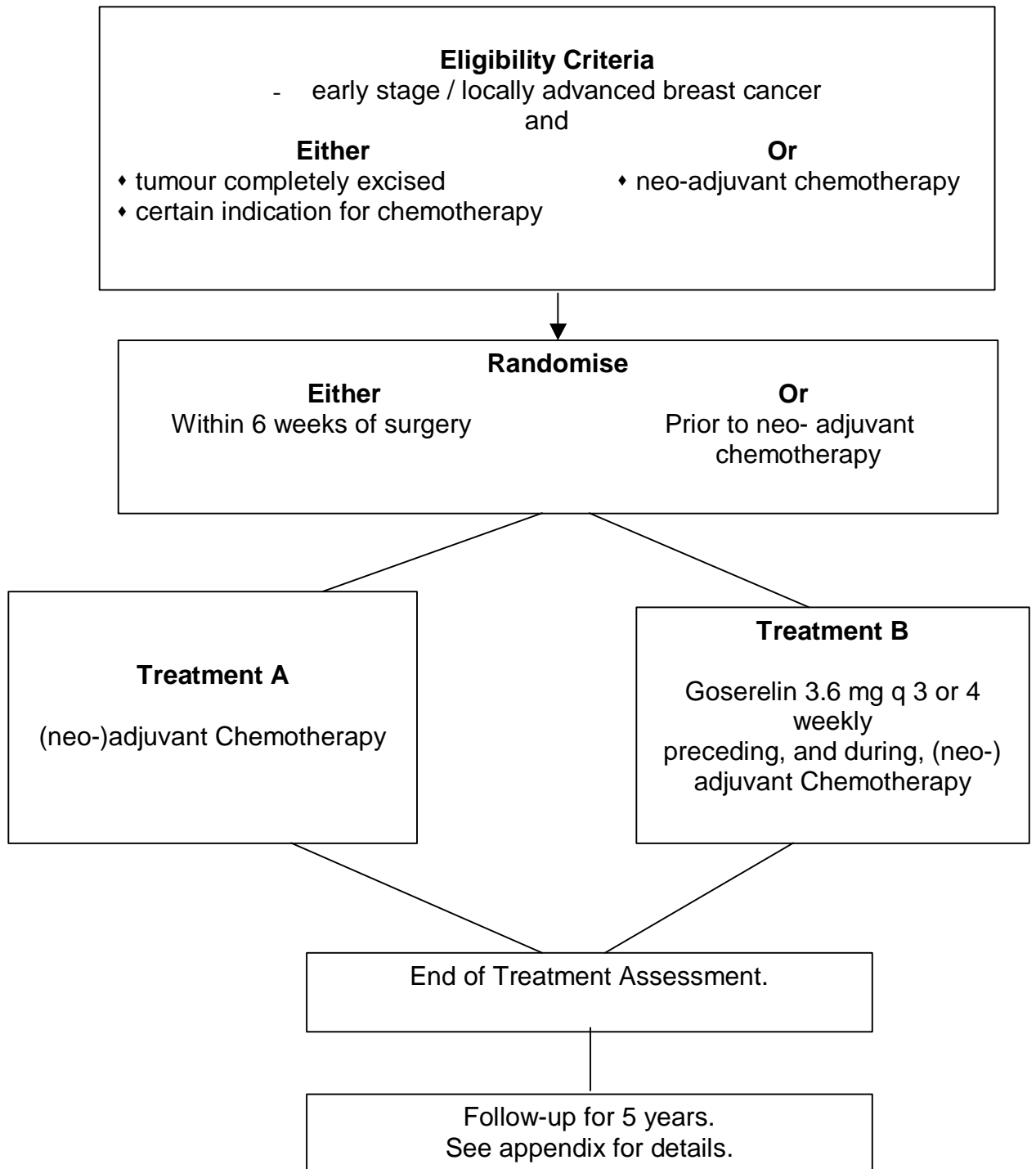
Approved

A handwritten signature in black ink, appearing to read 'R Leonard', written over a horizontal line.

Date 27th October 2004

Professor RCF Leonard
Principal Investigator

Study Schema



CONTENTS	PAGE
1.0 STUDY SYNOPSIS	4
2.0 INTRODUCTION	5
2.1 ADJUVANT CHEMOTHERAPY	5
2.2 CURRENT STUDY	6
3.0 STUDY OBJECTIVES	7
3.1 PRIMARY OBJECTIVES	7
3.2 SECONDARY OBJECTIVES	7
4.0 STUDY POPULATION	7
4.1 INCLUSION CRITERIA	7
4.2 EXCLUSION CRITERIA	7
5.0 RANDOMISATION	8
6.0 PRE-TREATMENT EVALUATION	8
6.1 CLINICAL	8
6.2 PATHOLOGY	9
6.3 QUALITY OF LIFE – BASELINE MENOPAUSAL SYMPTOMS	9
7.0 STUDY DESIGN	10
7.1 STRATIFICATION	10
7.2 CHEMOTHERAPY	10
8.0 OTHER PRIMARY TREATMENT	10
8.1 SURGERY	10
8.2 RADIOTHERAPY	10
9.0 FOLLOW-UP	11
10.0 TRIAL ADMINISTRATION	11
11.0 STATISTICAL CONSIDERATIONS	12
12.0 END OF STUDY	12
12.0 PUBLICATION POLICY	13
13.0 TUMOUR TISSUE	13
REFERENCES	14
QUALITY OF LIFE SUB-STUDY	16
APPENDIX 1 – EVALUATION POINTS	24
PATIENT INFORMATION SHEET & CONSENT FORM	
GP LETTER	

1.0 STUDY SYNOPSIS

AIM

To prevent early menopause due to chemotherapy, using goserelin.

STUDY TITLE

Ovarian Protection Trial In Oestrogen Non-responsive Premenopausal Breast Cancer Patients Receiving Adjuvant or Neo-adjuvant Chemotherapy “OPTION”

INVESTIGATORS

Chief Investigator: Professor RCF Leonard (Singleton Hospital, Swansea)
Multicentre throughout the UK

OBJECTIVES

To assess the value of goserelin ovarian suppression in the prevention of chemotherapy-associated menopause in premenopausal women with early or locally advanced breast cancer.

DESIGN

Prospective, multicentre, randomised, open, comparative, parallel group study.

PATIENTS

- histologically confirmed breast cancer
- appropriate risk factors indicating need for adjuvant or neo-adjuvant chemotherapy
- fit to receive chemotherapy on either arm of the study
- premenopausal
- ER negative / poor and not candidates for adjuvant endocrine therapy
- adequate hepatic, renal and bone marrow function
- no prior chemotherapy or endocrine therapy
- no prior or concomitant malignancy (except basal cell carcinoma or in-situ carcinoma of the cervix)

SAMPLE SIZE

400 patients planned over a recruitment period of three years

TREATMENT REGIMENS

either

6-8 cycles of cyclophosphamide and/or anthracycline containing polychemotherapy. (This allows inclusion of hybrid regimes in which only 4 cycles may contain cyclophosphamide and/or anthracycline e.g. EC x 4 followed by Taxane x 4; FEC x 4 followed by Taxane x 4; E x 4 followed by CMF x 4)

or

same chemotherapy **preceeded by goserelin** with the goserelin continued to completion of chemotherapy

EVALUATION CRITERIA

Primary Endpoint

Rate of premature menopause.

Defined as menses stopping during a course of chemotherapy with no recovery for at least 12 months

Secondary Endpoints

QoL and incidence of menopausal symptoms in each arm

Bone mineral density loss

Hormone levels, including: FSH, LH, Oestradiol, β inhibin

Menstruation history (measured by patient keeping a menstrual diary)

Incidence of pregnancy

2.0 INTRODUCTION

2.1 Adjuvant chemotherapy

The 1992 overview of adjuvant chemotherapy for women with early breast cancer showed that treatment, in most cases with a combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), affords a modest, but clinically significant, improvement in survival¹. This was most apparent in pre-menopausal women with node-positive disease in whom the annual odds of recurrence were reduced by 36% and odds of death by 25%. Adjuvant chemotherapy is now accepted as standard treatment in premenopausal women with node-positive breast cancer. The overview has not, however, established the optimal drugs, doses and schedule for adjuvant chemotherapy. Evidence is accumulating however to indicate that anthracycline-based regimens may produce better outcomes especially for higher risk disease. This development is being further tested by the examination of the addition of taxoids for higher risk patients.

One of the major long-term side effects of chemotherapy is premature menopause and loss of fertility^{2,3,4}. The exact mechanism of chemotherapy induced ovarian failure is unknown. Ovaries can show a spectrum of damage from decreased number of secondary follicles to absent follicles with ovarian fibrosis. The action of a cytotoxic agent on the ovaries can work via impairment of follicular maturation and/or the depletion of primordial follicles. Alkylating agents such as cyclophosphamide are most commonly associated with gonadal damage. These agents do not act on a particular stage of the cell cycle and therefore do not need cell proliferation to work. It is believed that they may act on undeveloped oocytes and possibly pregranulosa cells of primordial follicles.^{5,6}

A review of ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer,⁵ found that the risk of gonadal damage was related directly to the age of the patient, with patients aged 40 and over having a consistently higher rate of premature menopause compared to those under 40 years of age. In the review of patients receiving mainly CMF type regimens, the average rate of premature menopause was 40% in women aged less than 40 years and 76% in those aged 40 and over.

There is some evidence that anthracyclines are less likely to produce premature menopause compared to classical alkylating agent based regimens like CMF. However, the length of regimens compared in this study were not comparable (AC x 4 vs CMF x 6)⁴. Nevertheless, typical regimens still induce premature ovarian failure rates of around 40% in populations where the median age is 40 years. The ovarian failure rates are again likely to be higher in older premenopausal women.

Morbidity of premature menopause

Premature onset of the menopause in a woman who is potentially cured from breast cancer may have other significant health and health economic consequences.

Within a year of the menopause, a significant degree of bone loss occurs, leading to an increased risk of osteoporosis, a major cause of morbidity in post-menopausal women.^{7,8,9} A recent study of premenopausal women who had been given chemotherapy showed bone mineral density loss to be correlated significantly to menstrual function after chemotherapy at 2 years, with patients who developed amenorrhoea having more marked bone loss than those with regular or irregular menstruation¹⁰.

There are also possible adverse effects on cardiovascular function. A number of studies have shown that women who have undergone early menopause had higher rates of coronary disease and poorer lipid profiles than women who retained ovarian function for longer.^{11, 12}

With the associated menopausal symptoms emerging at an early age, it is unsurprising to find evidence that premature ovarian failure is distressing psychologically and has a negative impact on sexual functioning^{13, 14}.

2.2 The current study

It has been proposed that treatment with a GnRH agonist alongside chemotherapy may mediate gonadal damage associated with chemotherapy, as GnRH agonists override the natural pulsatile GnRH frequency necessary for Luteinizing Hormone and Follicle Stimulating Hormone secretion. This could decrease the growth stimulation of rapidly growing germ cells¹⁵, and hence the cytotoxic effects of chemotherapy agents.

There is, however, some uncertainty over the exact mechanism involved. A very small study of patients with Hodgkin's disease¹⁶ found no benefits of giving buserelin prior to and during chemotherapy. However, there is evidence from a series of larger uncontrolled studies in lymphoma and breast cancer that indicates that goserelin may have a protective effect against chemotherapy-induced premature ovarian failure^{17, 18, 19}. Although fertility may still remain a problem¹⁹. These studies however, have not been randomised controlled trials, it is therefore necessary to undertake such a study.

The trial will test the following hypothesis:

"In women who require chemotherapy for operable hormone-insensitive breast cancer the use of goserelin may reduce the risk of premature ovarian failure"

Premature ovarian failure is defined as :-

Cessation of menstruation during chemotherapy, with no return of menses for at least 12 months.

3.0 STUDY OBJECTIVES

3.1 Primary objectives

- (i) To determine the impact of goserelin on the incidence of premature ovarian failure following chemotherapy for operable breast cancer, defined by clinical assessment and endocrine assay.

3.2 Secondary objectives

- (i) Quality of life and menopausal symptoms
- (ii) Bone mineral density loss
- (iii) Hormone levels, menstruation (using a menstruation diary kept by patients), pregnancy.

4.0 STUDY POPULATION

All premenopausal ER negative women who have had either mastectomy or breast conserving surgery for operable breast cancer, or are due to undergo neoadjuvant chemotherapy, may be considered for inclusion in the study.

4.1 Inclusion criteria

- (i) Histologically confirmed invasive, early operable or locally advanced breast cancer, stages I-III B (with N0-2)
- (ii) Complete excision of primary tumour, if being considered for adjuvant chemotherapy
- (iii) Suitable risk and fitness status for chemotherapy
- (iv) Premenopausal with regular menses in the 12 months up to time of surgery
- (v) No prior or concomitant invasive malignancy at any other site, except adequately treated basal or squamous carcinoma of the skin or in-situ carcinoma of the cervix
- (vi) No prior chemotherapy or endocrine therapy
- (vii) Women should be non-lactating, not pregnant, and using reliable methods of contraception for duration of chemotherapy.
- (viii) Written informed consent
- (ix) ER/PgR poor or negative (see definition on page 8) and not being considered for adjuvant endocrine therapy

4.2 Exclusion criteria

- (i) Failure to meet **any** of the above inclusion criteria
- (ii) Women with metastatic breast cancer including supraclavicular fossa metastases.
- (iii) ER/PgR +ve/moderate/rich or planned to have adjuvant endocrine therapy
- (iv) Patients should not receive endocrine therapy during or following chemotherapy.

5.0 RANDOMISATION

Patients will be randomised only if:

- **The investigator in charge is satisfied that the patient is eligible for the study**
- **Randomisation and treatment can start within 6 weeks of surgery.**

When written informed consent has been obtained from a woman who is eligible for the study the ISD Cancer Clinical Trials Team (formally the Scottish Cancer Therapy Network).

Randomisation Line should be contacted by:

1. telephone on **0131 - 275 - 7276** or **0131 – 316 - 4278** (Monday to Friday 9.00am to 5.00pm)

OR

2. fax on **0131 – 275 – 7512** (24-hour secure line)

At the time of randomisation the patient's details, disease and treatment characteristics will be requested. Eligibility criteria will be confirmed verbally.

Treatment will be allocated according to computer-generated lists.

6.0 PRETREATMENT EVALUATION

Staging investigations will be those that are standard practice at each institution.

6.1 Clinical

Pretreatment evaluation will include:

- History and physical examination,
- FBC,
- Biochemistry profile (including alkaline phosphatase - AST/ ALT, bilirubin, and creatinine),
- CXR and ECG,
- Hormone levels including :oestradiol , FSH, LH, β inhibin,

Bone Mineral Density will be measured at selected centres

- Bone mineral density (DXA scan) of the lumbar spine (L2-L4) and total hip (up to 3 months prior to or within 1 month of start of chemotherapy).
- Urinary N telopeptide – bone resorption marker and serum alkaline phosphatase

NB. High quality DXA scanning will be required with daily calibration records and quality assurance of DXA measurements.

6.2 Pathology

Pathology will be reported locally. Data to be collected should include the pathological size, type, histological grade, proximity to excision margins, oestrogen receptor status, presence of vascular +/- lymphatic invasion, number of lymph nodes positive and number examined, and the presence of extra-nodal tumour. Patients will be given information on, and asked to give consent for, use of their tumour tissue for future research.

Oestrogen receptor status for eligible patients will be defined as “poor” or “absent”

Immunohistochemical assay (using “H” score):

poor	=	< 100 (or Quickscore/Allred category < 6)
moderate	=	100 – 200 (or Quickscore/Allred category 6 or higher) EXCLUDES PATIENT
rich	=	> 200 – EXCLUDES PATIENT

6.3 Quality of Life - Baseline menopausal symptoms

Post surgery (or pre-chemotherapy for neo-adjuvant treatment) but prior to randomisation into the OPTION study, women will be given the FACT-ES to measure menopausal symptoms (see attached sub- protocol).

7.0 STUDY DESIGN

This will be an open, randomised multicentre study.

7.1 Stratification

Patients will be stratified by:

- age ≤ 40 and > 40
- centre of randomisation

7.2 Chemotherapy

Patients should start their allocated chemotherapy within 6 weeks of definitive surgery. Patients having neo-adjuvant chemotherapy should be expected to receive 6-8 cycles of chemotherapy containing cyclophosphamide and/or anthracycline in total. Patients who have adjuvant treatment following neo-adjuvant chemotherapy will remain in the same treatment arm throughout (i.e.+/- goserelin).

Patients will be randomised to receive either:

A 6-8 cycles of chemotherapy containing cyclophosphamide and/or anthracycline. (This allows inclusion of hybrid regimes in which only 4 cycles may contain cyclophosphamide and/or anthracycline e.g. EC x 4 followed by Taxane x 4; FEC x 4 followed by Taxane x 4; E x 4 followed by CMF x 4)

OR

B chemotherapy as A, **plus** goserelin 3.6 mg
Goserelin administration

The first goserelin injection to be given at least 1 week prior to chemotherapy, ideally goserelin should be started 2 weeks before the first chemotherapy, and continuing q 3 or 4 weekly until completion of chemotherapy). Goserelin should be given at least 4 weekly to maintain ovarian suppression. The last goserelin injection can be given up to 3 weeks before administration of the last cytotoxic drugs. For example 3 weeks before day 14 of oral CMF regimen, 3 weeks before day 8 of IV CMF and 3 weeks before Day 1 of a 3 weekly bolus regimen such as AC.

8.0 OTHER PRIMARY TREATMENT

8.1 Surgery

Primary surgery will be determined by the surgeon: either local excision or mastectomy combined with axillary clearance according to local practice. It is recommended that the excision margins be clear of tumour.

8.2 Radiotherapy

The precise timing of radiotherapy will be determined according to local practice, but the timing and extent of irradiation should be determined by each centre prior to starting the study

9.0 FOLLOW-UP

Clinical review at 6 month intervals for the first 2 years and at least 12 monthly for a further 3 years, and annually thereafter up to 5 years.

Hormone levels (including FSH, LH, β inhibin and oestradiol) after completion of cycle 3 and after final cycle (cycle 6 or cycle 8 depending on chemotherapy regime) at 9 and 12 months and annually thereafter up to 5 years. (Use of oral contraceptives should be documented). Patients will also be asked to maintain a menstruation diary for 24 months following the start of chemotherapy.

FACT-ES questionnaires will be administered at 3, 6, 12 18 and 24 months from the start of chemotherapy and then annually until 5 years. Patients who relapse will complete one final questionnaire, but will not be sent further follow up forms. (See attached sub-protocol).

In **selected centres** bone mineral density (by DXA-scan) will be measured at 12, 24 and 36 months. The urinary marker for bone resorption, N telopeptide, as well as serum alkaline phosphate, will be measured at 6, 12,18,24 and 36 months.

Investigations for distant relapse need be performed only as signs and symptoms indicate. First relapse in soft tissues should be confirmed histologically or cytologically.

Metastatic disease should be treated according to local practice.

- Blood serum and urine analyses.

All patients will have hormone levels measured. FSH, LH and oestradiol will be measured in local laboratories. However, beta-inibin will be analysed at a central laboratory in Edinburgh. For the beta-inhibin measurement a blood serum sample of 2ml will be required. This will be collected and stored locally at -20° C and shipped in batches approximately every 6 months to the central laboratory in Edinburgh.

For centres participating in the bone sub-study, serum alkaline phosphatase and urinary n-telopeptide will be measured. The serum alkaline phosphatase will be analysed centrally using serum collected for the beta-inhibin measurement. Urinary n-telopeptide will be stored locally at -20° C and transferred in batches approximately every 6 months to be analysed in a central laboratory in Sheffield.

10.0 TRIAL ADMINISTRATION

Serious Adverse and Serious Unexpected Adverse Event reporting will be co-ordinated by the ISD Cancer Clinical Trials Team. All events **MUST** be reported to the Trials Team immediately.

FAX Number: 0131 275 7512

Definition

A Serious Adverse Event, Serious Adverse Reaction or Unexpected Serious Adverse Reaction is any adverse event that at any dose:

- Results in death

- Is life-threatening*
- Requires in-patient hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in offspring of patient regardless of time to diagnosis).
- Is a cancer, or
- Is the result of an overdose (whether accidental or intentional)

Other important medical events that may not result in death, are not life threatening, or do not require hospitalisation may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above (excluding cancer or result of overdose).

* The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

** Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure, for continued observation. Hospitalisation for a pre-existing condition, including elective procedures, which has not worsened, does not constitute a serious adverse event.

The following list of adverse events/reactions are **expected** in patients receiving adjuvant chemotherapy for breast cancer in the OPTION trial and should be recorded as such and reported to the Trials Team.

Hospitalisation as a result of:

- neutropenia
- febrile neutropenia
- infections to Hickman line, catheter or wound
- pyrexia
- sore throat
- nausea or vomiting
- diarrhoea
- cellulitis
- mucositis

For patients receiving goserelin in the OPTION trial the potential **expected** adverse events/reactions include the following list. These events should be recorded as toxicities unless they fall into the definition of Serious Adverse Events detailed previously.

- lethargy,
- nausea and indigestion,
- weight gain

- breast swelling
- low mood
- allergic reactions
- temporary thinning of hair
- headaches.

All other SAE's will be treated as Suspected Unexpected Serious Adverse Events (SUSAR's). All SUSAR's when clarified as being Unexpected will be reported by the Trials Team to the Regulatory Authority (MHRA) and MREC in accordance with the guidelines in the European Directive on Clinical Trials

11.0 STATISTICAL CONSIDERATIONS

The rates of premature menopause are assumed to be 40-80% depending on age and drug regimen. For the purposes of the sample size calculation, the rates of premature menopause are assumed to be 40% in the under 40 age group and 80% in the over 40 age group (Bines et al, 1996). Reported rates of preservation of ovarian function using goserelin with chemotherapy in the 2 uncontrolled studies are around 80%, (possibly higher in the under 40's): i.e. rates of premature menopause with goserelin of around 20% or less.

Based on a one sided test with 5% false positive rate, the groups will require 190 and 150 patients respectively to have a 90% chance of detecting an absolute reduction in premature menopause rate of 20%, that is from 40% to 20% in the under 40 age group and from 80% to 60% in the over 40 age group. A total of 340 patients are therefore required, but the totals in the two age groups separately must be achieved. This figure will rise to 400, in order to account for an approximate 15% loss to follow up of patients.

11.1 Proposed analyses

For categorical endpoints (premature menopause, incidence of menopausal symptoms, quality of life measures), chi squared tests stratified by age group will be used. Proportions of patients in each treatment group, along with confidence intervals, will be reported for each endpoint.

For continuous endpoints (bone density reduction, other clinical results and quality of life measures), analysis of variance stratified by age group will be used, with appropriate transformations of variables. Mean values in each treatment group, along with confidence intervals, will be reported for each endpoint.

The first full analysis will be carried out when the primary endpoint for all patients has been recorded. This will be one year from the date of the last menstrual period of the last patient.

Analyses will be carried out by age group; the sample size allows adequate power for these comparisons.

11.2 Bone mineral density

Bone Mineral Density of the lumbar spine (L2-L4) and neck of femur (total hip) will be measured at selected centres. High quality DXA scanning will be required with daily calibration records and quality assurance of DXA measurements.

The measure for each patient is the percentage change in BMD from baseline to 2 years. This measure is assumed to be normally distributed with a standard deviation of 3.25^(19,20). A sample size of 100 patients per arm will be required to detect a difference of 1.5% between the two arms, with a 5% significance level and 90% power. An additional 15 patients per arm will be included at baseline to allow for loss to follow up.

12 END OF STUDY

For the purposes of Clinical Trial Authorisation (CTA) under the European Union Directive 2001/20/EC, the study is deemed to have ended 30 days after the last patient receives the last dose of the investigational medicinal product (IMP).

The duration of time for which patient follow up data will be collected is dependent on future funding arrangements. Current funding is secured for this to continue for 5 years after the start of the trial, and further funding will be sought for this to continue indefinitely.

For the purposes of Multi-Research Ethics Committee approval, the study end date is deemed to be the date of last data capture.

13 PUBLICATION POLICY

This study will be presented at appropriate scientific meetings and will be submitted for publication in a peer reviewed medical journal. Authors for any presentation will include the principal investigator, trial co-ordinators, statistician, representatives from ISD Cancer Clinical Trials Team and at least the highest 5 recruiting investigators. Other individuals who have made a substantial contribution to the design, conduct or analysis of the trial will be acknowledged.

The data generated in this trial remain the property of the Anglo Celtic Cooperative Oncology Group and no presentation or manuscript may be made without the agreement of the Group.

14 TUMOUR TISSUE

Although no pathology sub-studies are currently planned, patient information on future research on tumour tissue will be provided. Consent for such future research will also be requested. Any tumour tissue taken as part of this study shall be deemed the property of the Anglo Celtic Co-operative Oncology Group.

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QUALITY OF LIFE SUB-PROTOCOL

Lesley Fallowfield
Cancer Research UK Psychosocial Oncology Group
Brighton & Sussex Medical School
University of Sussex
BN1 9QG

1. Introduction

1.1 Quality of life assessment

There are now many novel endocrine therapies licensed for use with women who have breast cancer. Several clinical trials of adjuvant therapy comparing different drugs with the aim of determining efficacy, toxicity and overall general health and well-being are in progress or have recently reported. Publications containing the systematic collection of comprehensive subjective data to date are few thus little is known about the impact that hormone therapy exert on the quality of women's lives. This is an important area to investigate as it is known that the toxicity profile of different anti-oestrogens, progestins and aromatase inhibitors varies, and evidence is emerging that some are less benign than was originally thought.[1]

The side-effects of some endocrine therapies may be underestimated by healthcare professionals when their views are compared with those of patients.[2] However the side-effects of different treatments and the impact that these may have on quality of life (QOL) must be determined if informed choices about disease management are to be made. For example, menopausal symptoms may be considered too high a price for some women to pay in adjuvant therapy, especially if such treatment is still of unknown benefit in terms of preventing recurrence of the disease. Furthermore, without a comprehensive assessment of quality of life, it is difficult to know what supportive and ameliorative interventions may be needed to accompany the treatment found to be most efficacious in terms of treating breast cancer and preventing its recurrence. Most importantly, the magnitude of difference between treatment groups that may be expected in terms of QOL and the incidence of symptoms is likely to be much larger than the differences in survival.

1.2 Qol Measurement

Unfortunately, most existing quality of life instruments do not have an adequate range of items to provide a comprehensive assessment of the impact that hormone treatment has on different aspects of functioning and well-being. An endocrine subscale to accompany a well-validated QOL measure called the FACT-B (Functional Assessment of Cancer Therapy – Breast version) was developed specifically for use in trials using drugs likely to cause endocrine related symptoms.[3]

FACT-ES (Functional Assessment of Cancer Therapy - Endocrine Subscale version) consists of the FACT-B questionnaire plus an additional endocrine subscale. FACT-B (breast) consists of the FACT-G (general) QOL tool for cancer patients plus the Breast Cancer subscale.[4, 5] FACT-ES has been developed to measure QOL in patients receiving endocrine therapy for

breast cancer. This instrument (FACT-ES) should, therefore, be sensitive to QOL changes in patients in this trial. FACT-ES is currently available in English, French, Spanish, German, Italian and Dutch/Flemish.

The FACT-B + ES are currently being used in 2 major adjuvant trials – ATAC, and the Inter-Group Exemestane study.

The FACT-B (version 4) is a multi-dimensional self-report questionnaire measuring 5 domains: physical well-being, social well-being, emotional well-being, functional well-being, and breast cancer concerns. It has good psychometric properties, discriminates well between groups and is responsive to change. It is relatively simple and quick to complete, has been translated into many different languages and is being used in a large number of breast trials in the US and Europe.

2. Aims

To compare quality of life between those patients allocated to 6-8 cycles of cyclophosphamide and/or anthracycline containing polychemotherapy with those allocated to the above preceded by goserelin.

3. Trial Design

Patients will receive their randomised treatment and be followed up for 5 years or until confirmation of disease recurrence as detailed in the main protocol. This sub-protocol will assess the QOL in all consenting patients over this period and at recurrence, should this occur within the study period. Patients who are entered in to the main trial and who consent to participate in the QOL trial will be asked to complete a baseline QOL questionnaire before randomisation, at 3,6,12,18,24 months, and yearly thereafter until 5 years. Patients with recurrence will complete one further questionnaire one month post-recurrence.

3.1 Patient selection

The main trial is multi-centre, and all patients should be included in the QOL study. Patients must be informed of its existence pre-randomisation. It is important that the value and relevance of QOL data is explained carefully to participating patients so that they are motivated to comply with data collection. The need for good compliance must be stressed. The patients should be given a comprehensive information leaflet about the QOL study which they can take home with them. The researcher should also stress that the information is completely confidential. Therefore, if the patient has any medical problems, she should discuss them with the doctor or research nurse.

4. Trial Procedures

4.1 Baseline and Follow-up

All eligible patients in participating centres will be invited to take part in the study and to complete a baseline QOL questionnaire after a full explanation of the study by the doctor and or clinic nurse. If the patient does not wish to participate in the QOL study, this will be recorded, with reason.

For all other assessments, the questionnaires must be completed **before** seeing the clinician for the FU appointment and will be sent by post with a pre-paid envelope for the women to return to the co-ordinating centre. The main trial co-ordinator will inform the QoL co-ordinators of any protocol violations, withdrawals or recurrences.

4.2 Completion of the Questionnaire – instructions

- It must be completed by the patient herself
- It must be completed before any investigations or discussions about the status of the patient's disease with the clinic staff
- Help should not be given from relatives or clinic staff
- Only one answer to every question should be circled
- Completed baseline questionnaires should be placed by the patient in a sealed envelope and given to the appointed individual at the clinic for mailing to the Coordinating Data Centre

Following completion, the researcher must confirm verbally with the patient that the questionnaire has been completed fully.

5. Data Management

The data will be handled by the coordinator based at the University of Sussex

6 Inclusion Criteria

In participating centres, eligible patients are all patients who are:

- eligible for the main trial
- have given signed informed consent to participate in the QOL side-study

7 Endpoints

Primary endpoint

Change between baseline and follow-up Treatment Outcome Index (TOI) scores between both treatment arms.

Specific endpoints

- comparison of the TOI within each treatment arm
- comparison of the total ES score for each treatment arm
- comparison of individual items from FACT-ES comparison of total FACT-B scores
- comparison of total scores from individual subscales

The 23 item TOI is recommended as an efficient and precise summary measure of the physical and functional well-being of patients in clinical trials.[5]It comprises of a summary score of the following subscales:

- Physical well-being
- Functional well-being
- Breast cancer subscale

8 Sample Size

Recruitment will continue until approximately 400 patients have been entered .

The sample size to detect a difference in change from baseline and at each follow-up of 5 in the TOI between the two treatment arms requires 400 patients to have $(1-\beta) = 90\%$ and $\alpha = 0.05$. A difference of 5 is considered to be clinically relevant (Brady et al, 1997).

The analysis of the specific endocrine symptoms and most commonly reported troublesome symptoms will consider only items with an incidence of more than 10% in either of the treatment arms. In the comparison of the overall Endocrine Subscale score, $(1-\beta) > 90\%$ to detect a difference in 4 between the two groups, ie the upper one-sided 95% confidence interval for the difference between the overall ES score must be less than 4. When looking at specific proportions of patients with side-effects, this number will show a 15% difference with 90% power.

8 Statistical Analysis

8.1 Timing of Analysis

The formal analysis of the data from the QOL study will be performed at the same time as the final analysis of the main study.

Groups of patients will be compared at agreed timepoints and overall for differences in the parameters of interest (Cox et al, 1992). The treatment groups will be compared at the individual timepoints with appropriate adjustments being made for multiple comparisons. Because of the longitudinal nature of the data, an analysis which takes the repeated measures into account is also needed. A generalised linear modelling approach will be adopted (Agresti, 1989; McCullagh & Nelder, 1989; Liang & Zeger, 1986). This will allow the appropriate error distribution to be used and will enable the analysis to take account of important factors such as age, stage of disease, treatments received and other sociodemographic and clinical characteristics.

8.2 Statistical Considerations

The comparison of both treatment arms between baseline and at each FU is considered the primary comparison.

• Primary endpoint

Longitudinal change in TOI between baseline and follow-up time points between treatment arms. TOI = physical well-being + functional well-being + breast cancer scale.

• Secondary endpoints

- (i) Total ES score = sum of responses to all questions on the ES
- (ii) TOI within treatment arms
TOI = physical well-being + functional well-being + breast cancer scale
- (iii) Most commonly reported endocrine symptoms

8.3 Missing values

All reasonable efforts will be made to ensure correct completion of the QOL assessments. A full explanation will be given by the assigned researcher prior to administration of the baseline questionnaire.

For missing items the following procedures will be adopted:

- 1 If more than 50% of the subscale scores have been completed, the scores will be prorated. The sum of the subscale is multiplied by the number of items in the subscale. This is then divided by the number of items actually answered. This is an accepted way of scoring the subscales provided that more than 50% of the questions have been answered.

- 2 If 50% or more of the questions have not been answered, the subscale will be considered as missing.
- 3 If a response is missing to an ES question then 'missing' will be assigned .

9 Interim Analysis And Data Monitoring

Independent Data Monitoring Committee (IDMC)

The IDMC for the main trial will review the data from this side-study at the same time as the data from the main study.

10 Informed Consent And Ethical Issues

Before starting the QOL study, the investigator is responsible for obtaining local ethics approval for the study. The investigator is responsible for obtaining each patient's signed informed consent prior to the administration of the baseline QOL assessment.

1. Coster, S. and L. Fallowfield, *The impact of endocrine therapy on patients with breast cancer: a review of the literature*. *The Breast*, 2002. **11**: p. 1 - 12.
2. Fellowes, D., et al., *Tolerability of hormone therapies for breast cancer: how informative are documented symptom profiles in medical notes for 'well-tolerated' treatments?* *Breast Cancer Res Treat*, 2001. **66**(1): p. 73-81.
3. Fallowfield, L.J., et al., *Assesment of quality of life in women undergoing hormonal therapy for breast cancer: validation of an endocrine subscale for the FACT-B*. *Breast Cancer Research and Treatment*, 1999. **55**: p. 189 - 199.
4. Cella, D.F., et al., *The Functional Assessment of Cancer Therapy scale: development and validation of the general measure*. *J Clin Oncol*, 1993. **11**(3): p. 570-9.
5. Brady, M.J., et al., *Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument*. *J Clin Oncol*, 1997. **15**(3): p. 974-86.

Appendix 1

OPTION Study - Evaluation Points

		Following start of chemotherapy										
	Pre - treat	Chemotherapy + /- goserelin	3 months	6 months	9 months	12 months	18 months	2 yrs	3 yrs	4 yrs	5 yrs	
History	X											
Physical Exam	X			X		X	X	X	X	X	X	X
FBC	X											
Biochemistry (including) ▪ Alk Phos ▪ ALT/AST ▪ Creatinine ▪ Bilirubin	X											
CXR	X											
ECG	X											
Hormone levels ▪ Oestradiol ▪ FSH ▪ LH ▪ β inhibin	X			X after cycle 3	X after cycle 6 or 8	X	X		X	X	X	X
FACT - ES	X*			X	X		X	X	X	X	X	X
<u>Selected centres – bone sub-study</u>												
DXA scan	X					X		X	X			
Urinary N-telopeptide	X			X		X	X	X	X			
Alk Phos	X			X		X	X	X	X			

*FACT-ES to be administered pre-randomisation by the randomising centre.
All other questionnaires will be sent directly to patients by the co-ordinating centre at 3, 6, 12, 18, 24 months and annually up to 5 years. The first follow up questionnaire will be sent 3 months following the **start** of chemotherapy.

Menstruation Diary to be kept by all patients.