

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

**ANGLO CELTIC III
SPROG**

G-CSF (filgrastim or pegfilgrastim) secondary prophylaxis
in the chemotherapy of early breast cancer

**Trial Administration by: INFORMATION & STATISTICS DIVISION, CANCER
CLINICAL TRIALS TEAM (formerly The Scottish Cancer Therapy
Network)**

Study No: BR 0101

Study Title: Prospective randomised comparison of G-CSF (filgrastim or
pegfilgrastim) secondary prophylaxis versus conservative
management of chemotherapy-induced neutropenia to maintain
dose intensity in chemotherapy for breast cancer.

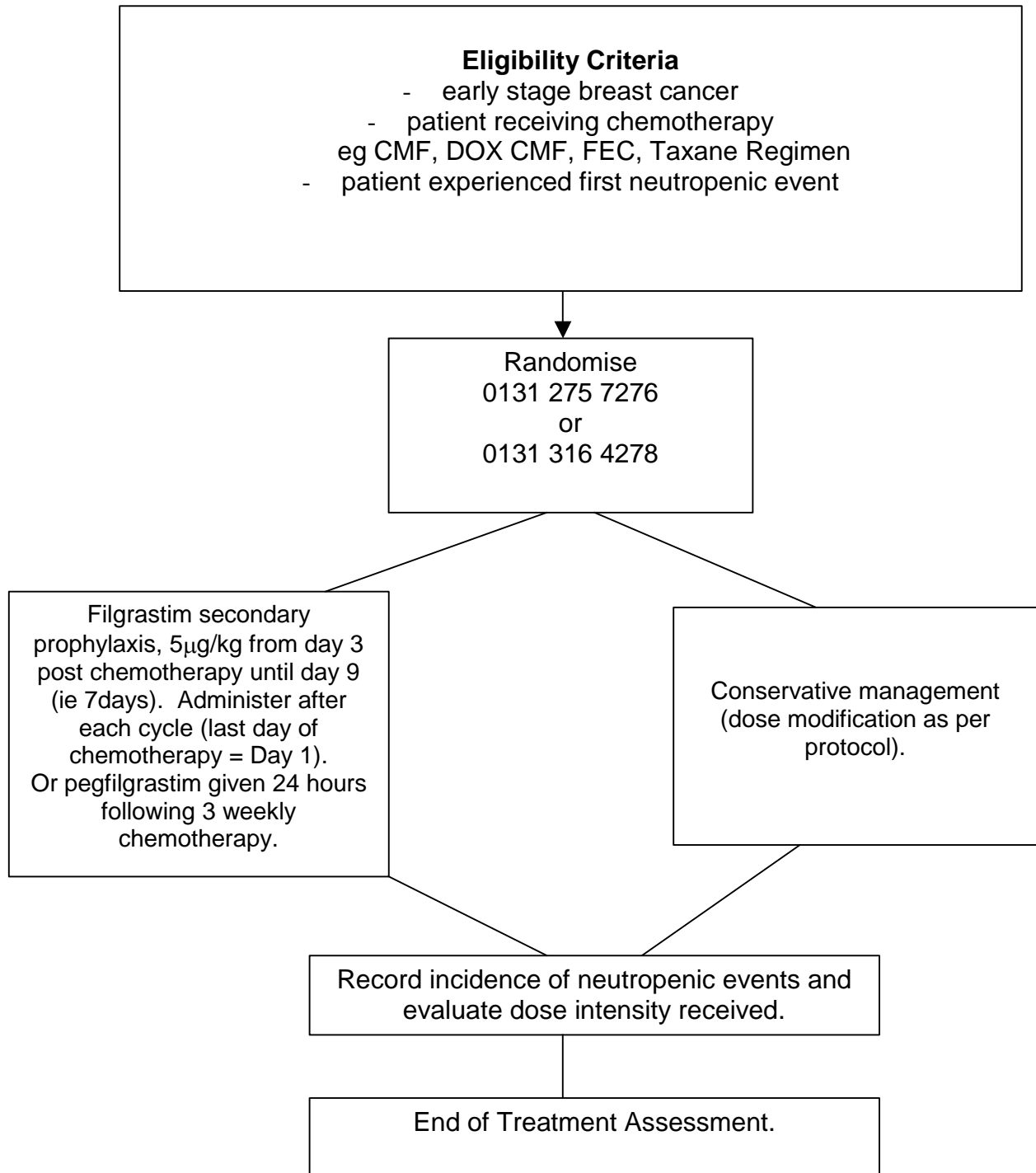
Approved



Date 02/02/04

Professor RCF Leonard
Principal Investigator

Study Scheme



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1.0 STUDY SYNOPSIS

1.1 PROJECT:

Secondary prophylaxis of neutropenia with G-CSF (filgrastim or pegfilgrastim).

1.2 STUDY TITLE

Prospective randomised comparison of G-CSF secondary prophylaxis versus conservative management of chemotherapy-induced neutropenia to maintain dose intensity in chemotherapy for breast cancer.

1.3 INVESTIGATORS

Multicentre throughout the UK.

Principal Investigator: Professor RCF Leonard (Western General Hospital, Edinburgh).
(Present address: Singleton Hospital, Swansea)

1.4 OBJECTIVES

To compare the effects of G-CSF secondary prophylaxis against standard management after the first neutropenic event (for definition see section 4.0) in achieving planned dose intensity of chemotherapy for early breast cancer.

1.5 DESIGN

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

1.6 PATIENTS

Inclusion criteria

- 18 years of age or older
- histologically confirmed invasive breast cancer
- no concomitant malignancy
- no prior chemotherapy (apart from the current regimen)
- previous neutropenic event (as defined in section 4) on chemotherapy and considered of suitable risk and fitness to continue chemotherapy
- written informed consent

Exclusion criteria

- patients with locally advanced or metastatic breast cancer including supraclavicular fossa metastases
- patients receiving sandwich/synchronous radiotherapy (defined as radiotherapy administered during a break in the chemotherapy regimen) - patients receiving concomitant radiotherapy during chemotherapy are not excluded
- previous exposure to G-CSF (filgrastim or pegfilgrastim)

1.7 SAMPLE SIZE

816 patients planned over a recruitment period of three years

1.8 TREATMENT REGIMENS

Standard chemotherapy as per local guidelines. Patients entered into TACT or TANGO protocols, or other protocols of licensed chemotherapies which do not exclude G-CSF usage, will be eligible for this protocol. Patients in the SECRAB trial will also be eligible. All chemotherapy to be dosed to Body Surface Area or weight (as per local practice).

1.9 G-CSF

Filgrastim to be dosed subcutaneously at 5µg/kg from day 3 post chemotherapy until day 9 (i.e. 7 days). For the purposes of dosing, the last day of chemotherapy administration shall be Day 1. Pegfilgrastim to be given subcutaneously in a single 6 mg dose 24 hours after the administration of chemotherapy. In the case of Day 1/Day 8 regimens, filgrastim shall be dosed starting on day 10 for 7 days. In the case of patients receiving CMF orally from Day 1 to 14 filgrastim shall be dosed starting on Day 16 for 7 days. Pegfilgrastim should not be given for Day 1 / Day 8 or CMF oral Day 1-14 regimens.

1.10 EVALUATION CRITERIA

Primary Endpoints

- Proportion of patients achieving $\geq 85\%$ of planned dose intensity in each arm
- Proportion of patients with at least one neutropenic event following randomisation
in each arm

Secondary endpoints

- Dose intensity achieved in each arm
- Cost of management

1.11 STATISTICAL METHODS

The number of patients required in order to detect a difference (with 80% power) between the two treatment groups, given that the underlying percentage of patients achieving 85% dose intensity in the treatment groups is 50% and 60% respectively, is 816.

It is assumed that the success of the two G-CSF formulations in improving relative dose intensity will be similar. The study is not designed to test any difference in outcome between filgrastim and pegfilgrastim.

The proportion of patients receiving at least 85% of the planned dose-intensity will be compared between treatment groups using logistic regression, adjusting for the randomisation stratification factors of centre and age. This is the primary analysis for this study.

The proportion of patients with at least one neutropenic event following randomisation will be analysed in a similar manner. In addition, the average number of neutropenic events per patient following randomisation will also be analysed.

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. In the first analyses of the Milan CMF adjuvant programme in the 1970's Bonadonna and colleagues indicated an association between actual dose-intensity achieved and outcome in terms of disease free and overall survival². The subset analyses showed that patients required to achieve a critical dose intensity of $\geq 85\%$ planned to derive benefit from adjuvant CMF. A subsequent report in 1995 on the same data set showed the same effect³. Other studies in both the setting of adjuvant therapy and treatment of metastatic disease have examined the issue of dose intensity within the conventional dose range but with inconclusive results. Evidence is accumulating however to indicate that anthracycline-based regimens particularly when relatively dose intense may produce better outcomes especially for higher risk disease^{4,5,6}.

A recent audit of neutropenia in the adjuvant setting found that a wide variety of chemotherapy regimens are being used in the UK⁷. The majority of patients received CMF based chemotherapy and 40% had anthracycline based treatment. 29% of patients had neutropenic complications during their treatment, leading to dose reductions, delays and in a few cases, hospitalisations. This meant that a third of patients did not achieve 85% of the planned dose intensity. Importantly 3% of CMF patients and 9% of patients receiving anthracycline-based therapy were unable to achieve even 70% dose intensity. The risk of having a subsequent neutropenic event, following a first event, was 56% in patients receiving CMF based therapy, and was 72% for anthracycline based regimens. This suggests that treatment with G-CSF may be most effectively targeted if it is given to patients who have already experienced a neutropenic episode i.e. secondary prophylaxis⁸.

***N.B. Neo-adjuvant patients are now eligible for the SPROG trial
(following amendment 01, which was MREC approved 16/01/02.)***

2.2 The current study

The trial will test the following hypothesis:

"In women who require chemotherapy for early breast cancer, the use of G-CSF (filgrastim or pegfilgrastim) secondary prophylaxis as routine supportive treatment after chemotherapy, in patients who have already had one neutropenic event (requiring dose modification or hospitalisation) will improve overall received dose intensity when compared to patients receiving standard conservative management".

There is evidence which shows that if patients on chemotherapy do not receive 85% of their original planned dose at the planned time due to toxicities, there can be an adverse effect on survival.

The trial is NOT powered to detect an effect on survival or disease-free survival. It is merely to see whether the use of G-CSF improves the ability to maintain dose intensity.

The adverse events patients may experience will vary according to the chemotherapy schedule – this will be a clinical decision by individual doctors. However, one of the common side effects of chemotherapy is neutropenia. The research question is whether G-CSF support can help to maintain the dose intensity of a chemotherapy regimen following an initial neutropenic event.

Data on adverse events will be collected in both arms of the trial. Patient survival will also be monitored for up to 10 years.

3.0 STUDY OBJECTIVES

3.1 Primary objectives

- (i) To determine the impact of G-CSF secondary prophylaxis on the delivered dose-intensity of chemotherapy for early breast cancer by assessing the proportion of patients achieving $\geq 85\%$ of planned dose intensity in each arm.
- (ii) To determine the proportion of patients who experience at least one neutropenic event following randomisation in each arm.

3.2 Secondary objectives

- (i) Dose intensity achieved in each arm.
- (ii) Cost of management.

4.0 STUDY POPULATION

All women over the age of 18 years of age who have histologically confirmed invasive breast cancer, including neo-adjuvant patients, may be considered for inclusion in the study. Patients should only be randomised after they have experienced a neutropenic event on chemotherapy. Patients entered onto other protocols including TACT or TANGO, will also be eligible for this study once they have met the inclusion/exclusion criteria. Patients receiving CMF orally from Day 1 to 14 will be eligible.

Definition of a neutropenic event

1. Hospitalisation due to neutropenia
2. ANC \leq 1.5 and considered sufficiently low to require a treatment delay or a dose reduction \geq 15% of planned dose.

4.1 Inclusion criteria

- (i) 18 years of age or older
- (ii) Histologically confirmed invasive breast cancer
- (iii) No concomitant malignancy
- (iv) No prior chemotherapy apart from the current regimen (prior tamoxifen does NOT exclude a patient from the study).
- (v) Previous neutropenic event on chemotherapy (as defined in section 4.0) and considered suitable risk and fitness status to continue chemotherapy
- (vi) Written informed consent

4.2 Exclusion criteria

- (i) Failure to meet **any** of the above inclusion criteria
- (ii) Patients with locally advanced or metastatic breast cancer including supraclavicular fossa metastases
- (iii) Patients receiving sandwich/synchronous radiotherapy (defined as radiotherapy administered during a break in the chemotherapy regimen). Patients receiving concomitant radiotherapy during chemotherapy are not excluded
- (iv) Previous exposure to G-CSF (filgrastim or pegfilgrastim)

5.0 RANDOMISATION

Patients will be consented and randomised after the first neutropenic event defined as one or more of the following:

1. Hospitalisation due to neutropenia
2. ANC \leq 1.5 and considered sufficiently low to require a treatment delay or a dose reduction \geq 15% of planned dose.

When written informed consent has been obtained from a woman who is eligible for the study the Randomisation Line should be contacted by:

- (i) telephone on **0131 - 275 - 7276** or **0131 - 316 - 4278** (Monday - Friday 9.00 a.m. to 5.00 p.m.)

OR

- (ii) fax on **0131 - 275 - 7512** (24-hour secure line)

The Randomisation Checklist should be completed. Eligibility criteria will be confirmed verbally or alternatively the Randomisation Checklist can be faxed to the Information & Statistics Division (ISD), Cancer Clinical Trials Team .

Treatment will be allocated according to computer-generated lists held in the ISD, Cancer Clinical Trials Team . Patients will be allocated to receive either secondary prophylactic G-CSF or standard conservative management.

At the time of randomisation details of the patient's original planned chemotherapy should be entered into the Case Report Form.

6.0 STUDY DESIGN

This will be an open, randomised multicentre study comparing G-CSF secondary prophylaxis versus conservative management of chemotherapy-induced neutropenia in the maintenance of dose intensity in breast cancer patients receiving chemotherapy. Patients who satisfy the eligibility criteria and have experienced a neutropenic event will be randomised to 1 of 2 treatment groups in a 1:1 ratio as follows:

Treatment arm 1: Filgrastim 5 μ g/kg administered subcutaneously from day 3 until day 9 (where the final day of chemotherapy is Day 1).

Or

Pegfilgrastim 6 mg subcutaneous injection given approximately 24 hours after the administration of chemotherapy.

For patients receiving Day 1/Day 8 chemotherapy regimens, filgrastim will be given from Day 10 for 7 days. For patients receiving CMF orally from Day 1 to 14 filgrastim will be given from Day 16 for 7 days. Pegfilgrastim should not be given for Day 1/ day 8 or CMF oral Day 1-14 regimens.

Treatment arm 2: Conservative management as per normal site practice.

6.1 Stratification

Randomisation will be stratified by:

- (i) centre
- (ii) age ≤ 60 and > 60

6.2 Chemotherapy

Patients will receive chemotherapy as per local practice. All chemotherapy will be dosed by Body Surface Area or weight as per local practice.

ANCs will be measured;

- prior to starting chemotherapy
- day 7 or day 8 of Day 1/Day 8 regimens and
- on start day or day before next chemotherapy cycle

For patients receiving CMF orally from Day 1 to 14

ANCs will be measured:

- prior to starting chemotherapy
- on start day or day before next chemotherapy cycle

6.3 G-CSF (filgrastim or pegfilgrastim) secondary prophylaxis

G-CSF (filgrastim or pegfilgrastim) will be administered as secondary prophylaxis to patients randomised to receive this intervention. Secondary prophylaxis involves the administration of G-CSF (filgrastim or pegfilgrastim) in all remaining chemotherapy cycles after the cycle in which the first neutropenic event was recorded. The dose of filgrastim will be 5 μ g/kg administered subcutaneously from day 3 after the end of chemotherapy until day 9 (i.e. 7 days), or 6mg of pegfilgrastim given as a single subcutaneous injection approximately 24 hours after administration of chemotherapy.

NB. The final day of chemotherapy is Day 1 (for Day 1/Day 8 cycles, filgrastim shall be given from Day 10 for 7 days; for patients receiving CMF orally from Day 1 to 14 filgrastim will be given from Day 16 for 7 days).

The G-CSF to be used will be filgrastim or pegfilgrastim and will be provided at a discount from Amgen Ltd.

6.4 Antiemetics

Antiemetics will be given according to local practice. A suitable regimen would be:

Granisetron 1 mg po OR ondansetron 8mg iv)	prior to
Dexamethasone 8 mg iv)	chemotherapy
Dexamethasone 2 mg po tds)	for 3 days after
Domperidone 20 mg po prn)	chemotherapy

6.5 Antibiotic prophylaxis

Antibiotic prophylaxis shall be administered as per local practice. Every attempt should be made to be consistent in usage across both arms of the study.

6.6 Treatment modifications

The toxicities most likely to require treatment modification are prolonged myelosuppression, neutropenic sepsis and mucositis.

6.6.1 Myelosuppression

NB/ Every attempt should be made to maintain chemotherapy at full doses.

- (i) If day 1,8,22 etc $ANC \geq 1.5 \times 10^9/l$
 - no modifications required
- (ii) If day 1,8,22 etc $ANC \leq 1.5 \times 10^9/l$
 - delay treatment for 1 week
- (iii) If treatment delayed ≥ 2 weeks:
 - reduce dose of myelosuppressive therapies as appropriate (aim to maintain a consistent approach to reduction across both arms of the study).

If further delays, the patient may stop chemotherapy at the clinician's discretion but these patients will still be included in the analyses as randomised in line with an intention to treat policy.

6.6.2 Neutropenic sepsis

- (i) No dose modification is required for uncomplicated neutropenia except as described above for day 1 counts. Routine monitoring of nadir counts is not required.
- (ii) In the event of neutropenic sepsis reduce dose of myelosuppressive therapies as appropriate (aim to maintain a consistent approach to reduction across both arms of the study).

6.6.3 Mucositis

Mucositis may be minimised by careful mouth care with the routine use of bicarbonate mouth wash and nystatin suspension. Oral cryotherapy with ice chips administered for 20-30 minutes during and immediately after chemotherapy is also helpful. If despite these measures patients experience grade 3 mucositis, treatment should be modified:

- (i) Epirubicin/doxorubicin: 15% dose reduction
- (ii) CMF: add folinic acid rescue (15 mg qid x 6 doses, starting 24 hours post-chemotherapy)

Although folinic acid rescue need not be routinely prescribed, in patients who are receiving concomitant therapy with agents known to impair methotrexate clearance (e.g. NSAIDs) folinic acid is recommended as above.

6.7 Toxicity Reporting

Following each chemotherapy cycle a treatment toxicity report should be completed in the appropriate section of the case report form.

6.8 End of Treatment

At the end of chemotherapy the Treatment Summary page of the Case Report Form should be completed. Details of any concomitant radiotherapy and hormone therapy and patient survival data will be required for completion of this form.

7.0 RADIOTHERAPY

Patients undergoing breast-conserving surgery require radiotherapy to the breast. Patients receiving sandwich/synchronous radiotherapy (defined as radiotherapy administered during a break in the chemotherapy regimen) should be excluded from this study.

Patients who have had mastectomy are at risk of local relapse in view of their axillary node status and chest wall irradiation is advised. Radiotherapy to the chest wall should be given according to local practice e.g. in patients with large tumours or heavy nodal involvement.

Irradiation of the cervico-axillary canal is required if axillary surgery less than a level 2 clearance has been performed.

Chemotherapy will start before radiotherapy. The precise timing of radiotherapy will be determined according to local practice.

8.0 FOLLOW-UP

Data on adverse events will be collected in both arms of the trial. Patient survival will also be monitored for up to 10 years.

Details of hospitalisations and of laboratory tests, anti-infective medications and transfusions (both on an in-patient and out-patient basis) will be collected in the Case Report Form and combined with estimates of unit cost to enable the effect of differences in resource usage between the two arms on the cost of management to be estimated.

It is anticipated that a high proportion of patients involved in this trial will also be participating in other studies that require the completion of Quality of Life (QoL) questionnaires. It would be undesirable for patients to have to complete multiple QoL questionnaires, often of differing styles, therefore to limit patient confusion and maximise the validity of data collected in other studies, QoL questionnaires will not be completed as part of this trial.

9.0 TRIAL ADMINISTRATION

The study will be co-ordinated by the ISD, Cancer Clinical Trials Team .

10.0 STATISTICAL CONSIDERATIONS

10.1 Sample Size

The number of patients required in order to detect a difference (with 80% power) between the two treatment groups, given that the underlying percentage of patients achieving 85% dose intensity in the treatment groups is 50% and 60% respectively, is 816

10.2 General Considerations

All statistical testing will be performed with a 5% level of significance. No interim analyses are planned.

10.3 Endpoints

The primary endpoints are the proportion of patients with at least 85% dose-intensity and the proportion of patient with at least one neutropenic event.

Dose-intensity will be calculated over all chemotherapy cycles received by the patient, i.e. including those prior to randomisation. Relative dose intensity will be calculated using the following equation:

$$\frac{\text{Dose given}}{\text{Dose planned}} \quad / \quad \frac{\text{Actual course duration}}{\text{Planned course duration}}$$

Neutropenic event is defined as either;

- 1 Hospitalisation due to neutropenia, or
- 2 $\text{ANC} \leq 1.5$ and considered sufficiently low to require a treatment delay or a dose reduction $\geq 15\%$ of planned dose.

Only neutropenic events after randomisation will be included in the analysis.

10.4 Analysis Sets

The primary analysis set is the intention-to-treat set, which consists of all patients randomised to a treatment group. Other analysis sets may be examined but will be considered of a secondary concern.

10.5 Analysis Methods

The proportion of patients with at least 85% dose-intensity will be compared between treatment groups using logistic regression, adjusting for the randomisation stratification factors of centre and age. The interaction between treatment group, centre and age will be investigated. This is the primary analysis for this study. Other analyses may be performed to investigate the relationship between this endpoint and other factors and will be considered to be of secondary importance.

The proportion of patients with at least one neutropenic event following randomisation will be compared between treatment groups in a similar manner to above. In addition, the average number of neutropenic events following randomisation will be calculated for each patient and compared between treatment groups using appropriate statistical methods. Finally, the total number of neutropenic events across all patients following randomisation will be summarised for each treatment group.

For each endpoint, results for the two G-CSF formulations will be reported but no formal statistical comparisons will be made.

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To be on headed notepaper

Pegfilgrastim

PATIENT INFORMATION SHEET

A comparison of different ways of managing neutropenia during chemotherapy for breast cancer.

Study Protocol Number: BR 0101

You are being invited to take part in a research study. Before you decide to take part it is important for you to understand why the study is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and You'. This leaflet gives more information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London N16 0BW.

Thank you for reading this.

1. What is the purpose of the study?

Patients receiving chemotherapy for treatment of breast cancer sometimes have a reduction in the number of infection fighting blood cells (neutrophils or white blood cells) because of the drugs used. This can mean that they are more likely to suffer from infections and may have to be treated in hospital.

One way of helping to keep the number of white cells high is to reduce the dose of chemotherapy that is given, or to delay giving the dose until the white cells have recovered. This is normally what happens at the moment, but it can mean that you receive less of the drugs than originally intended.

This study will show if it is possible to use a drug called pegfilgrastim to increase the number of white cells in your blood so that the planned dose of chemotherapy can still be given.

There is some evidence which suggests that patients who receive their chemotherapy at up to 85% of the planned chemotherapy dose may be less likely to suffer disease relapse. At the moment the best way to ensure that patients get the planned dose, without experiencing severe side effects is not known. The purpose of this study is simply to examine the effect of pegfilgrastim on the ability to give the planned chemotherapy compared with the standard practice of your centre.

2. Why have I been chosen?

Your details have been reviewed by your doctor at the hospital, who thinks that you will be able to help with this study because your white cell count was low which means that your planned treatment has to be modified. We would like to invite you to take part in this study. This study will take place in approximately 25 centres in UK/Ireland. Approximately 800 patients will take part in this study.

3. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

4. What will happen to me if I take part?

If you agree to take part in this study you will be chosen at random (similar to tossing a coin) to be put into one of two groups. If you are in the first group you will be treated in the normal way. If you are put into the second group you will have 1 pegfilgrastim injection 24 hours after your chemotherapy. In both groups, your medical care will not be changed from normal. You will have a 50% chance of having the pegfilgrastim injections.

You can decide to stop the study at any time. This will not affect your future care in any way. You may also be taken out of the study by the doctor if he/she thinks it is needed.

Pegfilgrastim may be given to you outwith the study if this is the standard treatment in your hospital and your doctor thinks it would be appropriate.

5. What do I have to do?

You will be required to visit the hospital at the same time as you normally would for your treatment. There are no extra blood tests needed for this study. If you are asked to use pegfilgrastim, you will have to have an injection after each treatment cycle. This will be given the day after chemotherapy treatment. You may give these to yourself, or a nurse or partner can give it to you at home. We will teach you and/or your partner how to give the injections at home and give you information about storing pegfilgrastim in the fridge. The study will last for a variable length of time depending on how many chemotherapy treatments you need.

6. What is the drug or procedure that is being tested?

The drug tested in this trial is called pegfilgrastim. Although it is licensed and used in the UK, it is not routinely given in this way at the moment. This study will see if pegfilgrastim can help to increase your white cells and allow your doctor to give you your chemotherapy at the dose he/she intends, and at the time it was planned.

7. What are the alternatives for diagnosis or treatment?

You may choose not to participate in this study. Whether or not you participate you will receive all standard therapy and medical care that is provided for patients with a low white blood count due to chemotherapy. The usual way of treating patients who have a low white count, and who have had infection, is to delay, or reduce the dose of (or both) their chemotherapy. If you take part in the study, you may be treated in this way no matter which treatment group you have been put into.

8. What are the side effects of taking part?

The most common side effect of the pegfilgrastim is mild to moderate bone pain. This pain usually goes away after taking a pain reliever (eg Paracetamol). If you think you have experienced symptoms that are due to the pegfilgrastim treatment these should be reported to your doctor or nurse. Studies

have not shown any increase in the frequency of side effects that are common in people receiving chemotherapy, when they are using pegfilgrastim

The chemotherapy drugs that you are given can also cause some side effects. Your doctor will be able to give you more information on these side effects.

9. What are the possible disadvantages and risks of taking part?

If you are asked to use pegfilgrastim, you will have to have 1 injection after each cycle of chemotherapy. This will be given the day after chemotherapy treatment. Some people may find the injections slightly uncomfortable. Other than that, your treatment will be the same as if you were not taking part in the study.

10. What are the possible benefits of taking part?

We hope that the treatment will help you. However, this cannot be guaranteed. The information we get from this study may help us to show that pegfilgrastim can stop patients from getting a low white count, and will allow doctors to give their patients their chemotherapy as planned.

11. What if new information becomes available?

Sometimes during the course of a study, new information becomes available about the treatment/drug that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your doctor will make arrangements for your care to continue. If you decide to continue in the study, you will be asked to sign an updated consent form.

12. What happens if the research study stops?

Sometimes research studies may be stopped. If this happens in this study your doctor will tell you the reasons and you will be treated in the normal way.

13. What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this if you wish to complain about any aspect of the way you have been treated during the course of this study, the normal Health Service complaints mechanism may be available to you.

14. Will my taking part in this study be kept confidential?

Yes. Your name will be kept secret outside the hospital. You will be given a unique study number and this will be used to make sure that you cannot be identified outside the trial. Your medical records may be reviewed by a representative of the Information & Statistics Division, Cancer Clinical Trials Team (formerly Scottish Cancer Therapy Network), by your hospitals' local research ethics committee or by authorised representatives of drug regulatory authorities. Your doctor will inform your General

Practitioner that you are taking part in the study. This will be done with your consent as it is anticipated that the injections will be carried out at your home.

15. What will happen to the results of the research study?

It is likely results will be published in a reputable scientific journal when the study has been completed and the results have been analysed. Your identity will not be revealed in this document. You will be able to obtain a copy of the results from your doctor at the hospital.

16. Who is organising and funding the research?

The study is being organised by the Information & Statistics Division, Cancer Clinical Trials Team on behalf of the Anglo Celtic Cooperative Oncology Group and partly funded by Amgen Ltd.

Your hospital of treatment will be paid a small amount to help with administration costs for this study.

17. Who has reviewed the study?

This study has been reviewed and approved by the multi-centre research ethics committee of Scotland and by the local research ethics committee for your hospital.

18. Costs/Reimbursement

No additional visits to the hospital will be required for this study therefore you should have no extra costs, no arrangements have been made to cover out of pocket expenses.

19. Contact for further information

If you would like independent advice on this study before deciding if you would like to take part then please contact:- Dr Peter Johnston, Consultant Haematologist, Western General Hospital, Edinburgh. Tel: 0131 537 1000

Now or during the course of the study, if you have any needs or questions concerning this study or your rights as a patient or in case of emergency, you should contact: Dr David Cameron, Senior Lecturer in Medical Oncology, Western General Hospital, Edinburgh. Tel: 0131 537 1000. You will be given a copy of the information sheet and a signed consent form to keep. Finally we would like to thank you for taking the time to read this information sheet.

To be on headed notepaper

Filgrastim

PATIENT INFORMATION SHEET

A comparison of different ways of managing neutropenia during chemotherapy for breast cancer.

Study Protocol Number: BR 0101

You are being invited to take part in a research study. Before you decide to take part it is important for you to understand why the study is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and You'. This leaflet gives more information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London N16 0BW.

Thank you for reading this.

1. What is the purpose of the study?

Patients receiving chemotherapy for treatment of breast cancer sometimes have a reduction in the number of infection fighting blood cells (neutrophils or white blood cells) because of the drugs used. This can mean that they are more likely to suffer from infections and may have to be treated in hospital.

One way of helping to keep the number of white cells high is to reduce the dose of chemotherapy that is given, or to delay giving the dose until the white cells have recovered. This is normally what happens at the moment, but it can mean that you receive less of the drugs than originally intended.

This study will show if it is possible to use a drug called filgrastim to increase the number of white cells in your blood so that the planned dose of chemotherapy can still be given.

There is some evidence which suggests that patients who receive their chemotherapy at up to 85% of the planned chemotherapy dose may be less likely to suffer disease relapse. At the moment the best way to ensure that patients get the planned dose, without experiencing severe side effects is not known. The purpose of this study is simply to examine the effect of filgrastim on the ability to give the planned chemotherapy compared with the standard practice of your centre.

2. Why have I been chosen?

Your details have been reviewed by your doctor at the hospital, who thinks that you will be able to help with this study because your white cell count was low which means that your planned treatment has to be modified. We would like to invite you to take part in this study. This study will take place in approximately 25 centres in UK/Ireland. Approximately 800 patients will take part in this study.

3. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

4. What will happen to me if I take part?

If you agree to take part in this study you will be chosen at random (similar to tossing a coin) to be put into one of two groups. If you are in the first group you will be treated in the normal way. If you are put into the second group you will be asked to use filgrastim injections for 7 days after your chemotherapy. In both groups, your medical care will not be changed from normal. You will have a 50% chance of having the filgrastim injections.

You can decide to stop the study at any time. This will not affect your future care in any way. You may also be taken out of the study by the doctor if he/she thinks it is needed.

filgrastim may be given to you outwith the study if this is the standard treatment in your hospital and your doctor thinks it would be appropriate.

5. What do I have to do?

You will be required to visit the hospital at the same time as you normally would for your treatment. There are no extra blood tests needed for this study. If you are asked to use filgrastim, you will have to have 7 injections after each treatment cycle. These will start on the second day after your chemotherapy treatment and you will have an injection each day until the eighth day after your treatment. You may give these to yourself, or a nurse or partner can give them to you at home. We will teach you and/or your partner how to give the injections at home and give you information about storing filgrastim in the fridge. The study will last for a variable length of time depending on how many chemotherapy treatments you need.

6. What is the drug or procedure that is being tested?

The drug tested in this trial is called filgrastim. It has been used around the world for many years to treat many thousands of patients. Although it is used in the UK, it is not routinely given in this way at the moment. This study will see if filgrastim can help to increase your white cells and allow your doctor to give you your chemotherapy at the dose he/she intends, and at the time it was planned.

7. What are the alternatives for diagnosis or treatment?

You may choose not to participate in this study. Whether or not you participate you will receive all

standard therapy and medical care that is provided for patients with a low white blood count due to chemotherapy. The usual way of treating patients who have a low white count, and who have had infection, is to delay, or reduce the dose of (or both) their chemotherapy. If you take part in the study, you may be treated in this way no matter which treatment group you have been put into.

8. What are the side effects of taking part?

The most common side effect of the filgrastim is mild to moderate bone pain. This pain usually goes away after taking a pain reliever (eg Paracetamol) or after filgrastim treatment is stopped. If you think you have experienced symptoms that are due to the filgrastim treatment these should be reported to your doctor or nurse. Studies have not shown any increase in the frequency of side effects that are common in people receiving chemotherapy, when they are using filgrastim .

The chemotherapy drugs that you are given can also cause some side effects. Your doctor will be able to give you more information on these side effects.

9. What are the possible disadvantages and risks of taking part?

If you are asked to use filgrastim, you will have to have 7 injections (one per day for 7 days) after each cycle of chemotherapy. These will start on the second day after your chemotherapy treatment and you will have an injection each day until the eighth day after your treatment. Some people may find the injections slightly uncomfortable. Other than that, your treatment will be the same as if you were not taking part in the study.

10. What are the possible benefits of taking part?

We hope that the treatment will help you. However, this cannot be guaranteed. The information we get from this study may help us to show that filgrastim can stop patients from getting a low white count, and will allow doctors to give their patients their chemotherapy as planned.

11. What if new information becomes available?

Sometimes during the course of a study, new information becomes available about the treatment/drug that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your doctor will make arrangements for your care to continue. If you decide to continue in the study, you will be asked to sign an updated consent form.

12. What happens if the research study stops?

Sometimes research studies may be stopped. If this happens in this study your doctor will tell you the reasons and you will be treated in the normal way.

13. What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this if you wish to complain about any aspect of the way you have been treated during the course of this study, the normal Health Service complaints mechanism may be available to you.

14. Will my taking part in this study be kept confidential?

Yes. Your name will be kept secret outside the hospital. You will be given a unique study number and this will be used to make sure that you cannot be identified outside the trial. Your medical records may be reviewed by a representative of the Information & Statistics Division, Cancer Clinical Trials Team (formerly the Scottish Cancer Therapy Network), by your hospitals' local research ethics committee or by authorised representatives of drug regulatory authorities. Your doctor will inform your General Practitioner that you are taking part in the study. This will be done with your consent as it is anticipated that the injections will be carried out at your home.

15. What will happen to the results of the research study?

It is likely results will be published in a reputable scientific journal when the study has been completed and the results have been analysed. Your identity will not be revealed in this document. You will be able to obtain a copy of the results from your doctor at the hospital.

16. Who is organising and funding the research?

The study is being organised by the Information & Statistics Division, Cancer Clinical Trials Team on behalf of the Anglo Celtic Cooperative Oncology Group and partly funded by Amgen Ltd.

Your hospital of treatment will be paid a small amount to help with administration costs for this study.

17. Who has reviewed the study?

This study has been reviewed and approved by the multi-centre research ethics committee of Scotland and by the local research ethics committee for your hospital.

18. Costs/Reimbursement

No additional visits to the hospital will be required for this study therefore you should have no extra costs, no arrangements have been made to cover out of pocket expenses.

19. Contact for further information

If you would like independent advice on this study before deciding if you would like to take part then please contact:- Dr Peter Johnston, Consultant Haematologist, Western General Hospital, Edinburgh. Tel: 0131 537 1000

Now or during the course of the study, if you have any needs or questions concerning this study or your rights as a patient or in case of emergency, you should contact: Dr David Cameron, Senior Lecturer in Medical Oncology, Western General Hospital, Edinburgh. Tel: 0131 537 1000. You will be given a copy of the information sheet and a signed consent form to keep. Finally we would like to thank you for taking the time to read this information sheet.

Form to be on headed paper)

Study Number: BR0101

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: Prospective randomised comparison of G-CSF secondary prophylaxis versus conservative management of chemotherapy-induced neutropenia to maintain dose intensity in chemotherapy for breast cancer.

Name of Researcher:

1. I confirm that I have read and understand the information sheet dated 2nd February 2004 (version 9) for the above study and have had the opportunity to ask questions.

Please initial the box

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

Please initial the box

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Information & Statistics Division, Cancer Clinical Trials Team, from the hospital or local research ethics committee or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. I also understand that my General Practitioner will be informed about my participation in this study.

Please initial the box

4. I agree to take part in the above study.

Please initial the box

Name of Patient

Date

Signature

Name of Person taking consent
(if different from researcher)

Date

Signature

Researcher

Date

Signature

z//

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Sample Letter to GP

To be on headed notepaper

Dear Doctor

Re: MREC No

A prospective randomised comparison of G-CSF (Filgrastim or pegfilgrastim) secondary prophylaxis versus conservative management of chemotherapy-induced neutropenia to maintain dose intensity in chemotherapy for breast cancer.

Your patient has experienced a neutropenic event whilst receiving chemotherapy for her breast cancer. She is therefore eligible and has agreed to participate in this large, multi-centre, randomised trial which aims to compare G-CSF secondary prophylaxis versus conservative management of chemotherapy-induced neutropenia to maintain dose intensity of her chemotherapy.

Your patient has been randomised to receive filgrastim. This means that she will receive filgrastim as secondary prophylaxis in all remaining chemotherapy cycles after the cycle in which the first neutropenic event occurred. The dose will be 5µg/kg administered subcutaneously from day 3 after the end of chemotherapy until day 9 (i.e. 7 days).

NB. The final day of chemotherapy is Day 1 (for Day 1/Day 8 cycles, filgrastim shall be given from Day 10 for 7 days; for patients receiving CMF orally from Day 1 to 14 filgrastim will be given from Day 16 for 7 days).

OR

Your patient has been randomised to receive pegfilgrastim (a long-acting form of G-CSF). This means that she will receive pegfilgrastim as secondary prophylaxis in all remaining chemotherapy cycles after the cycle in which the first neutropenic event occurred. The dose will be 6mg given as a single injection 24 hours after the administration of chemotherapy.

OR

Your patient has been randomised to receive conservative management as per our normal site practice.

If you require any further information or advice concerning the study or concerning the management of your patient please contact me on

Patient name:

Hospital number:

Yours sincerely

Name of Investigator