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Research Article

Examining Chemotherapy-Related Cognitive Changes in Colorectal Cancer Patients: A Feasibility Trial

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Abstract

Introduction: Research suggests that chemotherapy may be related to decline in patients' cognitive functions.

Objectives: To assess the feasibility and acceptability of a multi-site study designed to examine the nature and extent of chemotherapy-related cognitive changes in colorectal cancer patients.

Method: Data was collected over 8 months using objective and self-reported measures of cognitive functioning and self-reported quality of life, fatigue and mood questionnaires. The assessment battery was administered pre- and mid-chemotherapy treatment to a consecutive sample of colorectal cancer patients across three London-based NHS Trusts. Participants included patients who had undergone colorectal surgery and were scheduled to have adjuvant chemotherapy treatment, or no further cancer treatment.

Main outcome measures: Recruitment procedures, rate of recruitment, suitability of exclusion/inclusion criteria, acceptability of data collection procedures and the battery, and attrition rates.

Results: From 1 April 2014 to 1 December 2014, 42 eligible participants were invited to take part in the trial. Of the 17 that completed pre-chemotherapy assessments, only 1 withdrew at follow-up due to reasons of ill health from disease recurrence. All participants completed the entire battery and indicated that they found the trial acceptable.

Conclusions: What went wrong: Strained researcher resources; loss of eligible participants to competing studies, restrictive upper age limit.

Possible solutions: Removal of upper age limit, an increased dedicated research team to increase rate of recruitment.

The large multi-site study is feasible with suggested amendments and is acceptable to patients and medical teams. Acceptability of trial to medical teams is further evidenced by requests of collaboration from two additional London based NHS Trusts.

Lessons learned: This feasibility trial provides evidence to other researchers designing similar studies in this area of an acceptable design and the need for appropriate funding for resources to recruit large enough consecutive samples of patients with solid tumour cancers

Introduction

Research suggests that chemotherapy may be related to a decline in cognitive functions such as memory and attention in some solid tumour cancer patients [1-4]. However, the presence, extent and course of any cognitive decline and whether or not it causes observable difficulties for patients remain unclear.

The majority of research studies to date have explored cognitive function in cancer patients after treatment has been completed [5]. Few studies have measured patients' cognitive function prior to the commencement of chemotherapy treatment and hence these studies do not have any baseline. Measuring cognitive function both before and after chemotherapy would make it possible to identify changes occurring during treatment and the duration of such treatment related changes.

An additional limitation of existing studies is that they have often lacked a comparison group (e.g. cancer patients who have not required chemotherapy) against which to compare cognitive function scores. Furthermore, the majority of cognitive

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research to date has focussed on female breast cancer patients. This has precluded an exploration of gender differences in relation to cognitive decline.

This study examines the feasibility of a protocol designed to examine the nature and extent of chemotherapy related cognitive changes in colorectal cancer ("CRC") patients (the "Protocol") [6]. Given the proposed scale of the study, it was considered appropriate to first conduct a feasibility trial (the "Trial"). It is good practice and important for research to carry out this type of feasibility trial prior to a full study [7]. The Trial would determine the resources required, whether the Protocol could be implemented as designed, or whether any alterations were necessary.

Objectives

Bowen et al [8] suggested eight general areas of focus that may be addressed by feasibility studies for proposed interventions. This was narrowed to four areas, as the Trial did not involve an intervention. (See Table 1, which defines how the areas of focus correspond to the Trial objectives).

The primary objectives of this Trial were to evaluate:

Recruitment procedures: In order to assess the maximum number of eligible participants, the most efficient procedures for recruitment were examined so as to establish and confirm the:

a) Extent to which the suggested recruitment procedures could be carried out as proposed

b) Similarities/differences in recruitment procedures between the three collaborating London based NHS Trusts (the 'Trusts')

c) Extent to which the clinical teams were supportive of the Trial

d) Ease of identifying eligible participants

e) Number of eligible participants per Trust.

Participant numbers: A critical issue was to examine the patient flow as determined by the consent rate of eligible participants entering this Trial in order to [9-11]:

Areas of Focus	Trial Objectives
Implementation (*the extent to which and the likelihood that the proposed multi-site study can be fully implemented in accordance with the Protocol*[1])	To what extent can the recruitment procedures be carried out as proposed? How willing are the clinical teams to facilitate and/or help recruit participants?
Practicality (*an exploration of the extent to which the Protocol may be delivered given available resources and time*[1])	Capacity of staff and logistics.
Acceptability (*how will the individual recipients (both patients and clinicians) react to the procedures and assessments*[1])	Acceptability of the data collection procedures and assessments to participants and clinicians?
Practicality	Attrition rates and time needed to collect and analyse data

[1]These are an adaptation of the definitions of each area of focus provided by Bowen et al, 2009

Table 1: Areas of Focus and Trial Objectives.

a) Determine the time necessary to recruit a sufficient sample

b) Make projections of the funding and resources needed to execute an appropriately powered multi-site study

c) Assess the suitability of inclusion/exclusion criteria.

Methodology/testing of data collection procedures and assessments: The piloting and assessing acceptability of the proposed technique of data collection [11] according to the Protocol, was important, as each participant was required to undergo a series of neuropsychological assessments and questionnaires (the "Battery").

Attrition rates: Similar research in breast cancer treatment suggests that attrition rates in longitudinal cohort studies range from 10% to 33% [12-15]. The extent to which these data would be generalisable to the proposed population who differed in age, gender, cancer type and course of treatment needed to be determined.

Ethical Approval

Ethical approval was obtained from the NHS Health Research Authority – NRES Committee South-West Cornwall & Plymouth in August 2013. As part of the approval process it was also necessary to obtain a patient's perspective and view of the proposed Trial. Therefore prior to commencing the Trial an advertisement was posted on the Macmillan's Cancer Support online community noticeboard (http://community.macmillan.org.uk/volunteering/noticeboard/default.aspx) and also on Beating Bowel Cancer's patient forum (http://www.beatingbowelcancer.org/forum), asking bowel cancer patients for their general opinions and thoughts on the Trial. The feedback received was positive. The study was considered to be "worthwhile".

Methods

In accordance with the Protocol, a longitudinal cohort study was implemented between 1 April 2014 and 1 December 2014 inclusive (the 'Trial Period'). Data was collected at:

- 'T1" post-surgery and prior to chemotherapy treatment
- 'T2" twelve to fourteen weeks after first scheduled chemotherapy treatment or 3 months post surgery (as appropriate)
- 'T3" three months after last scheduled chemotherapy treatment or approximately 6 months after T2 (as appropriate).

Participants

During the Trial Period, a consecutive sample of patients between the ages of 18 and 65, diagnosed with resectable CRC under the care of the CRC team were invited to participate.

Eligibility required patients to:

a) Have undergone colorectal surgery

b) Not have distant metastases; and

c) Require adjuvant chemotherapy treatment or no post-surgery treatment at all.

Patients with prior exposure to chemotherapy and those with significant psychiatric or medical comorbidities, which might affect ability to participate in the Trail, were excluded. Patients could not enter the Trial if they were unable to read and speak English.

Measures

The measures used are detailed in the Protocol [6].

Trial sample size

Extrapolating from the Protocol's power calculation and assuming a total sample size of 156 participants (78 per group) to be recruited over 18 months, an average of eight to ten patients per calendar month would need to be consented into the Trial.

Procedure

Potential participants were identified at the weekly CRC multi-disciplinary team (MDT) meetings held by each Trust.

Proposed recruitment procedures were as follows:

- At the participant's post-surgery follow-up appointment, typically three to six weeks after surgery ('OPA'), a member of the clinical team would introduce the researcher to the patient.
- The researcher would then provide the patient with written information about the Trial and answer questions raised.
- The patient would be asked if they would be willing to be contacted by telephone within a few days to discuss participation in the Trial. Patients who agreed to participate were then given an appointment to meet with the researcher either at the hospital or at home.

Those patients who did not wish to participate after reviewing the information sheets were not contacted again.

T1 assessments were planned to take place one to two weeks after the OPA and prior to the patient's first scheduled chemotherapy appointment or at a parallel point in time for the surgery-only group. Eligible participants were to be consented into the Trial immediately prior to T1. The assessments for T1 were expected to take each participant approximately 2 hours and 30 minutes to complete.

At the end of T1 participants were advised that they would be contacted again via telephone within approximately 10 to 12 weeks to arrange the meeting for T2. T2 would be scheduled for between 12 and 14 weeks after T1 or between cycle 6 and cycle 7 in the case of the chemotherapy treatment group and at a parallel point in time for the surgery only group.

The same process would be utilised for T3, with assessments carried out at participants' homes at approximately 3 months after the final scheduled chemotherapy treatment, and at a similar point in time for the surgery-only participants.

Based on the sample size calculation set out in the Protocol, the attrition rate could not exceed 22%.

Results

Recruitment procedures

The Trial indicated that procedures were quite similar at each Trust. At all Trusts the surgery-only follow-up appointments were more difficult to determine than the chemotherapy patients.

Participant numbers

Recruiting from three Trusts (six hospital sites), attending all MDT's, surgical and chemotherapy clinics whilst also carrying out all assessments exceeded the single researcher's capacity; indicating that recruitment would require additional staff.

The surgery only control group proved more complex to recruit, as there were multiple surgeons at each hospital site making it difficult to identify all follow up OPAs. In addition eligible surgery-only participants approached by the researcher often refused participation as they asserted that they had completed treatment.

Forty-two CRC patients across 3 Trusts were invited to participate during the Trial Period, twenty-three agreed and were consented; however five changed their minds prior to completing T1. At the end of the Trial Period eighteen had completed T1 and eight T2. Seventeen of the eighteen remained in the Trial after the Trial Period and completed T2. One patient withdrew after T1 due to the appearance of a new cancer lesion. The sample at T1 was made up from 38.8% males and 61.2% females with a mean age of 59.7% years.

Fourteen of the eighteen participants (77.8%) were in the chemotherapy group. However, one participant was advised to start chemotherapy treatment several weeks after completing T1 and another that started in the chemotherapy group stopped treatment after three cycles but continued in the Trial.

The rate of recruitment was approximately three per month once the recruitment procedures and working practices were established. This indicated that significantly more research capacity and sites were required as it would take approximately four years to recruit the 156 participants required with the current resource.

Inclusion/exclusion criteria

Eligible participants were lower in number than expected in part due to the inclusion/exclusion criteria, age and also competing trials. Following ethics approval the age criterion was altered to have no upper age limit to increase recruitment.

Methodology/Testing of data collection procedures and assessments

All participants completed the full Battery. Consequently the administration of the Battery was deemed appropriate.

A suitable testing environment was achieved by administering the Battery in a quiet space both at the hospitals and participants' homes.

At the completion of T1, participants were asked how they felt about the assessments. The comments made suggested that participants in both groups found the design, methods and procedures employed in the Trial appropriate.

ID 1: *"this was very enjoyable"*

ID 14: *"It took my mind off things, I enjoyed doing it"*

Attrition rates

During the Trial Period, attrition at T2 was very low with only 1 participant withdrawing due to ill health. All participants who completed T1 expressed a desire to continue in the Trial. Continued participation in the Trial would suggest that the proposed multi-site study is worthwhile.

Conclusions

The Trial provided evidence that the Protocol is feasible subject to increasing the number of researchers and collaborating sites both to improve recruitment rates and to prevent clashes with assessments.

One possible solution to improving the rate of recruitment was implemented during the Trial Period, by removing the upper age limit for eligible participants. This has since made a difference in number of consented participants.

The number of patients consenting to the Trial and a very low attrition rate suggests that many CRC patients are willing to participate and that the Battery is feasible and well tolerated by patients.

Another strength of the proposed Protocol evidenced during the Trial was the acceptability of the multi-site study to clinical teams demonstrated by requests of collaboration from two additional London based NHS Trusts. In addition, the Trial provides valuable information to other neuropsychologists interested in the cognitive effect of chemotherapy treatments in the form of a realistic plan. It also makes clear the requirement for sufficient funding and resources. This could in turn allow for a large multi-institutional study across several English speaking cities and/or countries. All institutions could administer the same neuropsychological battery to a very large number of solid tumour cancer patients and pool all data as suggested by the International Cognition and Cancer Task Force [4].

One potential limitation of the proposed study however, is that the majority of patients had never heard of chemotherapy related cognitive changes, which may cause concern and/or priming effects. However, in the event that priming does occur it will do so in both the chemotherapy group and the surgery only group, so useful comparisons between the groups of any observed objective changes may still be made. In addition, any possible priming effects will not prohibit the researchers from being able to examine the impact of chemotherapy related subjective cognitive changes on the individuals' quality of life.

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