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Original article

Pilot randomised study of early intervention based on tumour markers in the follow-up of patients with primary breast cancer

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ABSTRACT

Background: This pilot study aimed to test the possibility of therapeutic benefit imparted by early intervention based on sequential tumour marker (TM) measurements during follow-up of primary breast cancer (PBC) patients.
Methods: Patients with oestrogen receptor positive PBC with no clinical and/or radiological evidence of metastases were recruited and followed-up 3-monthly with clinical assessment and TM (CA15.3 and CEA) measurements. The clinical team was blinded to the TM results. Asymptomatic patients who developed raised TMs (based on pre-defined cut-offs) were randomised to either 'treatment change' (either start or change of adjuvant endocrine agent to another agent) or 'no change' (control). Patients who developed symptomatic metastases came off the study. The primary and secondary endpoints were intervals from randomisation to symptomatic metastases and to last follow-up/death respectively.
Results: Eighty-five patients (median age = 54 years (30–72)) were recruited with a median follow-up of 81 months (1–124). Sixteen patients were randomised as described. There was no significant difference (treatment change versus no change) with regards to interval from randomisation to symptomatic metastases – 23 (2–62) and 22 (1–63) months respectively ($p = 0.9$), as well as interval from randomisation to last follow-up/death – 36 (7–63) and 37 (10–63) months respectively ($p = 0.9$).
Conclusions: Despite long follow-up (up to 10+ years), this small study has thus far shown no significant difference in outcome. However, we have confirmed the feasibility of this study design but a larger study will be required to show if there is a benefit to this approach.

Introduction

Tumour markers (TMs) are known to be elevated in the majority of patients with symptomatic metastatic breast cancer [1]. CA 15-3 assay testing MUC1 mucin (a membrane glycoprotein in epithelium of breast duct), and CEA (a glycoprotein found normally in embryonic entodermal epithelium) are the most widely used serum markers in breast cancer and their elevated levels appear to predict adverse outcome in primary breast cancer [2]. CA 15-3 is generally regarded as the more sensitive and specific of the two markers. Repeatable objective measures of these TMs reflect a dynamic change in the bulk of disease in the body, and thus their levels during treatment reflect response to therapy [1]. Elevation of these tumour markers has been thought to be an adverse prognostic factor in recurrent disease. In a recent study, Lee et al. investigated the prognostic value of CA 15-3 and CEA levels at diagnosis of systemic recurrence [3]. Over a 10-year period 351 systemic recurrences were identified in patients being followed-up with tumour markers subsequent to primary breast cancer treatment. Elevation in tumour marker was found to be an independent prognostic factor on multivariate analysis suggesting its association with tumour burden in recurrent disease.

Nicolini A et al. in their earlier retrospective study involving 384 primary breast cancer patients undergoing post-operative follow-up along with TM measurements, showed that the lead time from TM increase to the appearance of clinical and/or radiological signs of metastases was significantly longer for the group treated early at the time of TM rise compared to those not treated (13.5 ± 10 vs 3.4 ± 2.8 months respectively; $P < 0.001$) [4]. For patients treated

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'early', the survival curves up to 30 months after salvage treatment and up to 72 months after mastectomy showed greater survival than those for the patients treated later (42.9% vs 13.6% and 42.9% vs 22.7% respectively; $P = 0.04$ in both instances).

A Cochrane review published in 2005 included a pooled analysis of four randomised controlled trials and it failed to show added advantage for more aggressive follow-up with tumour markers and radiology over routine clinical and mammographic follow-up with regard to overall and disease free survival in patients with primary breast cancer [5]. However, this study did not taken into account the role of tumour markers and its value in prolonging the symptom free interval to metastatic disease.

We hypothesise that TMs may be elevated prior to symptomatic metastasis, and introduction of a systemic therapy such as an endocrine agent e.g. tamoxifen or aromatase inhibitors (AIs), could prolong the asymptomatic period in oestrogen receptor positive (ER+) breast cancers and could eventually prolong survival.

The study was initiated to pilot the concept of early treatment intervention, based on sequential TM measurements in patients with ER+ primary breast cancer, treated by surgery, who were undergoing follow-up. The primary endpoint of the study was symptomatic metastasis free interval (from randomisation to symptomatic metastasis) and the secondary endpoint was overall survival following randomisation.

Patients and methods

Clinical methods

Patients were recruited into the study from February 1999 to March 2000 and the last follow-up was June 2009. The eligibility criteria are shown below.

Inclusion criteria:

a) Patients with primary breast cancer proven on histology/cytology who had surgery with or without neoadjuvant or adjuvant radiotherapy or systemic therapies (i.e. endocrine therapy and/or chemotherapy) and undergoing routine clinical follow-up.
b) Patients whose primary tumour was ER+ or unknown.
c) No evidence of overt symptomatic metastatic disease.

Exclusion criteria:

a) History of another malignancy, excluding basal cell carcinoma or in situ cervical neoplasia.
b) Patients who were pregnant.
c) Patients who were identified to be an infectious risk (i.e. carriers of hepatitis B, acquired immune deficiency syndrome virus).

Patients who met the above criteria and who consented to take part in the study were followed-up with clinical assessment every three months in a dedicated research clinic according to the protocol shown in Fig. 1. Mammographic examinations were performed as per unit guidelines for all primary breast cancer patients. In addition, blood samples were collected for measurements of CEA and CA15.3. These TM results were blinded to the clinician who reviewed the patients in the clinic, and was reviewed by a dedicated chemical pathologist. If a significant elevation was detected in either TM (>6 ng/ml for CEA or >35 U/ml for CA15.3), this measurement was repeated after a further two weeks to confirm a persistent elevation.

Those patients who showed significant, persistent elevation of one or both of the TMs were randomised to either treatment change or no treatment. Patients found to have raised TMs and randomised to treatment change were seen in the clinic with a dedicated breast care research nurse for re-staging and treatment change as shown in Fig. 1. Patients were followed-up until development of symptomatic metastasis or death.

All patients were informed at the beginning of the study that they would be blinded to the results of TMs so as to reduce the anxiety in the control group. Only patients being offered a change of treatment underwent full staging investigations and were therefore aware that their TMs had risen. Initial staging investigations included bone scan, chest radiograph, liver ultrasound examination and blood tests (full blood count, liver function tests). Patients who developed symptoms of metastatic disease, had full work-up for metastatic disease as appropriate and if found positive were treated and followed-up in a dedicated advanced breast cancer clinic.

For those patients who were randomised to have treatment change, postmenopausal patients who had been receiving tamoxifen had it changed to anastrozole and vice versa. Premenopausal patients received goserelin alone as first choice followed by goserelin plus tamoxifen or goserelin plus anastrozole (if currently on goserelin plus tamoxifen).

Laboratory methods

Assays of both CA15.3 and CEA were carried out using automated kits in the Department of Clinical Pathology, Nottingham University Hospitals.

CA15.3 levels were measured using the commercially available automated system AxSYM® (Abbott, USA). The assay was based on Microparticle Enzyme Immunoassay (MEIA) technology which used a solution of suspended, submicron sized latex particles to measure analytes. The particles were coated with a capture molecule specific for the analyte being measured. The effective surface area of microparticles increased assay kinetics and decreased assay incubation time.

Reactants (115D8 antibody and DF3 antibody, both mouse monoclonal) and sample for one assay were transferred to a reaction vessel in which the reagents and samples were combined and then incubated to allow the reactants to come to a reaction temperature. The reaction mixture was transferred to an inert glass fibre matrix. Irreversible binding of the microparticles caused the immune complex to be retained by the glass fibres while the reaction mixture flowed rapidly through the large pores in the matrix.

An alkaline phosphatase labelled conjugate was added to the glass fibre matrix prior to the addition of 4-methylumbelliferyl phosphate (MUP). The conjugate catalysed the hydrolysis of MUP to methylumbelliferone (MU). Measurement of the fluorescent MU as it was generated on the matrix was proportional to the concentration of the analyte in the test sample.

Measurement of CEA was carried out using the commercially available Automated Chemiluminescence System ACS: 180 (Chiron, USA). The system was a two-site sandwich immunoassay using direct chemiluminometric technology, which used constant amounts of two antibodies: (1) in the lite reagent, a purified polyclonal rabbit anti-CEA antibody labelled with acridinium ester; and (2) in the solid phase, a monoclonal mouse anti-CEA antibody covalently coupled to paramagnetic particles.

Ethics & statistical methods

Ethical approval for the study was obtained from local research ethics committee prior to the commencement of study. The Statistical analysis was performed with the help of statistical Package for Social Sciences version 16 (SPSS version 16.0, Chicago, Illinois,