OPTIMA prelim: a randomised feasibility study of personalised care in the treatment of women with early breast cancer

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Scientific summary

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Background

Breast cancer is the most common cancer in the UK and the second most frequent cause of cancer death in women. The treatment of primary breast cancer, which is undertaken with curative intent, includes local and systemic therapies. Decisions on adjuvant chemotherapy are informed by an individual's risk of developing future metastatic disease, which is a function of tumour stage and biology.

A molecular classification first proposed in 2000 that divides breast cancer into four main intrinsic subtypes has transformed thinking about the disease. Subsequently, several gene expression signatures or multiparameter assays that predict risk of recurrence and death, or which classify breast cancer into subtypes, have been developed to guide the use of adjuvant chemotherapy. The best known, Oncotype DX® (Genomic Health Inc., Redwood City, CA, USA), provides a numerical 'recurrence score' (RS), which predicts residual risk for patients with oestrogen receptor (ER)-positive human epidermal growth factor receptor 2 (HER2)-negative breast cancer following endocrine treatment.

The Oxford Overview, a meta-analysis of randomised controlled trials (RCTs) in early breast cancer, suggests that the relative benefit of chemotherapy is independent of tumour biology. However, other evidence suggests that a subset of ER-positive HER2-negative breast cancer is insensitive to chemotherapy, although it is not possible to identify individual patients reliably by conventional clinical criteria. Studies in which Oncotype DX was performed on retrieved tumour blocks from participants in two historical chemotherapy trials showed that the relative benefit of chemotherapy varied according to the RS. This indicates that Oncotype DX can identify patients who are unlikely to benefit from chemotherapy, irrespective of risk from other clinical factors. Evidence from other multiparameter assays supports this conclusion.

The Optimal Personalised Treatment of early breast cancer usIng Multiparameter Analysis (OPTIMA) trial seeks to advance personalised treatment by establishing an appropriate and effective method of multiparameter analysis to identify which women with ER-positive HER2-negative early breast cancer are likely to benefit from chemotherapy, and those who are not. The study population would ordinarily be offered chemotherapy by either virtue of axillary lymph node involvement or tumour size. The OPTIMA trial is an adaptive trial that allows more than one technology to be evaluated. This report describes the feasibility phase, OPTIMA prelim.

Objectives

OPTIMA prelim had three objectives:

1. to establish acceptability to patients and clinicians of randomisation to test-driven treatment assignment compared with usual care
2. to establish efficient and timely sample collection and analysis essential to the delivery of multiparameter test-driven treatment
3. to evaluate the performance and health economics of alternative multiparameter tests to determine which technology(s) should be evaluated in the main OPTIMA trial.

The criteria for meeting these objectives, prespecified in the protocol, were:

- recruitment of 300 patients in 2 years from the first centre opening to recruitment, and, for the final 150 patients, (1) patient acceptance rate of at least 40%; (2) recruitment taking no longer than 6 months; and (3) chemotherapy starting within 6 weeks of signing the OPTIMA prelim consent form for ≥ 85% of chemotherapy-assigned patients
- identification of multiparameter test technology suitable for validation in the main trial.

Methods

Women aged ≥ 40 years with ER-positive HER2-negative early breast cancer and with 1–9 involved axillary nodes or, if node negative, a tumour of ≥ 30 mm in diameter were randomised to one of two treatment options. Option 1 (control arm) was standard treatment consisting of chemotherapy followed by endocrine therapy. In option 2 (experimental arm), an Oncotype DX test was performed on the resected tumour; patients with a RS of > 25 were assigned chemotherapy followed by endocrine therapy, and those with a RS of ≤ 25 were assigned to endocrine therapy alone. Chemotherapy was selected from regimens commonly used in the NHS. Referring centres were asked to specify intended chemotherapy at patient registration. The study was partially blinded so that neither patients nor referring centres were aware of whether chemotherapy was assigned through treatment option 1 or option 2.

Confirmatory retesting of ER and HER2 status was performed in the central laboratory on all consenting patients. Patients were randomised once eligibility was confirmed.

The OPTIMA trial is investigating 'less treatment than usual care'; thus, recruitment was likely to be difficult. The cancer advocacy group Independent Cancer Patients' Voice (ICPV) was consulted about study design and a representative was included in the Trial Management Group (TMG). ICPV facilitated three patient focus groups to explore attitudes towards the study.

The OPTIMA prelim study included an integrated qualitative recruitment study (QRS), designed to explore the recruitment process and provide evidence for improvements. The QRS was conducted in three phases. Phase 1 sought to identify and understand recruitment difficulties. Interviews were conducted with members of the TMG and research staff at participating centres. Audio-recordings were made of consultations when the OPTIMA prelim was explained to patients and transcribed for analysis, maintaining patient confidentiality. Phase 2 involved sharing phase 1 findings with the TMG and working collaboratively to design and deliver interventions to optimise recruitment and informed consent. Phase 3 evaluated the impact of the QRS, mapping QRS interventions and recruitment figures, and assessing changes in recruiter practice.

To evaluate candidate tests for use in the main study, additional multiparameter assays were performed on stored tumour blocks, irrespective of patient randomisation. Assays provided either a numerical risk score and predefined risk categorisation or assignment to a molecularly defined intrinsic subtype, or both.

Results were analysed to determine how the assays assigned tumours into risk groups and/or subtypes, and how these assignments differed between assays. The kappa coefficient and associated 95% confidence interval (CI) were used to assess agreement between tests. The predicted benefits of endocrine therapy with or without chemotherapy individualised to patients were estimated using the two predictive nomograms, 'Adjuvant! Online' version 8.0 (Adjuvant! Inc., San Antonio, TX, USA) and 'PREDICT' version 3, and two additional models developed specifically for this analysis. The additional models assumed the relative benefit of chemotherapy is either constant for all patients, independent of multiparameter assay result, or that it varies according to the RS.

An economic model comprising a time-dependent discrete-state transition model (modified Markov model) was developed for the analysis. This was used to estimate mean differences in clinical effects, including life-years and quality-adjusted life-years (QALYs), and costs for a hypothetical cohort of women with ER-positive, HER2-negative, lymph node-positive breast cancer using either Adjuvant! Online or the constant and variable benefit models. The cost-effectiveness analysis was conducted in accordance with the specifications of the National Institute for Health and Care Excellence reference case.

To characterise overall uncertainty in the output measures, a probabilistic sensitivity analysis was conducted using Monte Carlo simulation. Value-of-information analysis was performed to set priorities for further research into cost-effectiveness of multiparameter assays in the NHS.

Results

Recruitment

OPTIMA prelim opened to recruitment in September 2012. The database was locked on 3 June 2014, with 350 participants registered and 313 randomised into the study. The last 150 patients were recruited within 6 months at a rate of 28 per month. The average recruitment rate was 0.8 patients per open centre per month in the final 6 months of recruitment (0.7 over the entire recruitment period).

A total of 968 patients were listed in the screening logs, 795 of whom were deemed eligible. Of the 750 patients invited to participate in the OPTIMA trial, 350 consented to join the study. This equates to an overall 47% acceptance rate. The median time between patients giving consent and allocation of treatment was 20 days (interquartile range 16–23 days). The proportion of chemotherapy-assigned patients starting treatment within 6 weeks was 91% over the whole recruitment period and 92% within the last 6 months. All three prespecified feasibility criteria were therefore met.

A total of 35 hospitals participated in the study. Centres were selected by invitation in six main geographical clusters across the UK. Centres within each cluster included a mixture of cancer centres and district general hospitals, to ensure that feasibility could be demonstrated in a representative selection of UK centres.

A total of 12 out of 325 (3.7%, 95% CI 1.7% to 5.8%) consenting patients, for whom central review of receptors was performed, were deemed ineligible after central retesting of their tumour ER and HER2 status. Reasons included discrepancy in HER2 status ($n = 6$), tumour heterogeneity ($n = 2$) and discrepant ER status ($n = 4$, one of which was borderline positive according to local pathology).

Randomised patients were well balanced by age, menopausal status, tumour characteristics (grade, histological subtype), tumour size and lymph node status.

Patient and public involvement

Three patient focus groups facilitated by members of ICPV were held, the final one taking place 7 months after the study opened. All three groups reviewed the patient information sheet (PIS) and consent form. The study was acceptable to the majority of participants. Some had clear preference for chemotherapy, as that is what had been offered, and some discussed how they felt about not being offered chemotherapy. The trial design using a 'test' to decide treatment was acceptable and most felt that a personalised approach using multiparameter tests to be a preferred option. Comments made in the groups resulted in a revision of the PIS and contributed to the 'tips and guidance' document, which was an output of the QRS.

Qualitative recruitment study

A total of 14 semistructured interviews were conducted with research staff across six centres. Eight telephone interviews with research nurses were also conducted to understand the recruitment pathway for each centre. Thirty-six consultation recordings were obtained from 29 patients, involving 12 recruiters from all geographical clusters.

Analysis of interview transcripts identified several key challenges to recruitment, particularly difficulties in eligibility processes and clinician–patient communication. The latter included the quality and clarity of explanations of the trial design and trial-specific processes. These had potential to limit the number of patients approached, and/or ran the risk of threatening the trial's acceptability to patients.

These observations led to a series of QRS interventions in phase 2, which took place between July 2013 and January 2014. These included facilitating discussions about eligibility criteria with the TMG and at visits to recruiting centres, revision of the PIS, development and circulation of recruitment 'tips and guidance' sheets, delivery of group feedback meetings to address concerns collaboratively, and delivery of individual confidential feedback and support.

Although it is difficult to assess the distinct impact of the QRS among other variables potentially influencing study progress, recruitment improved as OPTIMA prelim progressed. Qualitative evidence suggests that QRS interventions had an impact on some clinicians' practices. The QRS has identified key recruitment issues that will be incorporated into the main OPTIMA trial.

Pathology study

A total of 313 randomised patients were eligible for inclusion at the cut-off of 3 June 2014, from whom 302 samples were available for analysis. Data are available for: Oncotype DX, MammaPrint and BluePrint® (Agendia Inc., Irvine, CA, USA), Prosigna™ (NanoString Technologies Inc., Seattle, WA, USA), IHC4, IHC4 automated quantitative immunofluorescence (AQUA®) (NexCourse Breast™, Genoptix Inc., Carlsbad, CA, USA) and MammaTyper® (BioNTech Diagnostics GmbH, Mainz, Germany).

Key findings were that for those assays that provided risk categorisation, 18% of tumours were considered high risk by Oncotype DX, 39% by MammaPrint, 34% by Prosigna, 28% by IHC4 and 18% by IHC4 AQUA. Despite the largely similar proportions in the risk categories, there was substantial disagreement between tests at an individual tumour level, with agreement between all five tests in only 39% of cases. For individual test comparisons, the highest kappa value was 0.60 between IHC4 and IHC4 AQUA, and the lowest was 0.33 between IHC4 and MammaPrint.

Of the three assays that assigned subtype, the proportion of tumours classified as having a (favourable) luminal A phenotype was 61% for BluePrint, 60% for Prosigna and 62% for MammaTyper (combined low-risk luminal B and luminal A); the great majority of the non-luminal A tumours were classified as luminal B. Similar to risk categorisation, agreement between all three tests at an individual tumour level was limited to only 59% of cases. The best agreement was between BluePrint and Prosigna, but the kappa value was 0.55, indicating only modest concordance. The lowest kappa value of 0.39 was for comparison between MammaTyper and MammaPrint.

Economic analysis

The base-case analysis included Oncotype DX, MammaPrint and Prosigna but excluded IHC4, MammaTyper and IHC4 AQUA. Inclusion criteria required both a defined test cost and adequate evidence for analytical and clinical validity, which were not available for all tests.

Multiparameter test-directed chemotherapy is expected to be cost-effective for all tests, although there remains uncertainty. With a willingness-to-pay threshold of £20,000 per QALY, the probability that multiparameter testing is more cost-effective than giving chemotherapy to all patients ranged from 77% (MammaPrint) to 79% (Oncotype DX and Prosigna). The differences in both the expected QALYs between the alternative tests and the expected overall costs were small. The probability of tests being cost-saving compared with chemotherapy for all patients was 53% for Oncotype DX, 39% for MammaPrint and for 68% Prosigna.

The estimates of the value of further research for Oncotype DX, MammaPrint and Prosigna are sufficient to justify studies capable of comparing long-term survival outcomes when using tests to direct chemotherapy. It should be noted that from the perspective of the NHS, the value of information for further research into Prosigna is higher than for the two other assays that were evaluated in this study. The analyses showed that uncertainty in the cost-effectiveness of tests is attributable not only to the performance of each of the tests but also the implications for long-term outcomes.

The recommendation of Prosigna as most valuable for further research withstood testing of the main assumptions around the survival of patients after cancer recurrence and also when considering other candidate or emerging tests such as IHC4 AQUA, IHC4 and MammaTyper. Further sensitivity analyses need to be performed to understand which model parameters are driving the costs and value of information.

Conclusions

- OPTIMA prelim succeeded in its aim of demonstrating that a large-scale study of multiparameter test-directed chemotherapy allocation in a high-risk population of patients with ER-positive HER2-negative cancer is feasible in the UK.
- Receptor determination (ER and HER2) is accurate in local centres in this patient population with an acceptable predicted error rate of 3.7%.
- Patient and public involvement and the QRS have contributed substantially, although in an unquantifiable manner, to the success of the project and should continue into a large-scale study.
- There is considerable discrepancy between the outputs of a selection of multiparameter assays performed on individual participant tumour blocks.
- There is considerable uncertainty regarding the cost-effectiveness of all tests considered. There is substantial value to the UK NHS in comparative research into all tests, although Prosigna may currently be considered the highest priority.

Trial registration

This trial is registered as Current Controlled Trials ISRCTN42400492.

Funding

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