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Problems of variable biomarker evaluation in stratified medicine research—A case study of ERCC1 in non-small-cell lung cancer

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ABSTRACT

Objectives: Consistency of procedures for the evaluation of a predictive biomarker (including sample collection, processing, assay and scoring system) based on adequate evidence is necessary to implement research findings in clinical practice. As a case study we evaluated how a particular predictive biomarker, ERCC1, was assessed in research on platinum-based chemotherapy in non-small-cell lung cancer and what motivated the choice of procedure.
Materials and methods: A systematic review of studies completed since 2007 and ongoing was undertaken. Questionnaires on details of ERCC1 evaluation procedures and the rationale for their choice were sent to contacts of identified studies.
Results: Thirty-three studies of platinum-based chemotherapy in non-small-cell lung cancer using ERCC1 were identified. A reply to the questionnaire was received for 16 studies. Procedures for ERCC1 evaluation varied substantially and included reverse transcriptase quantitative polymerase chain reaction (nine studies), immunohistochemistry (five studies) and other methods (multiple methods–two studies, NER polymorphism–one study). In five studies ERCC1 use was planned, but not undertaken. In nine data was insufficient to identify the procedure. For each assay there was variation across studies in the details of the laboratory techniques, scoring systems and methods for obtaining samples.
Conclusions: We found large variation across studies in ERCC1 evaluation procedures. This will limit the future comparability of results between these different studies. To enable evidence-based clinical practice, consensus is needed on a validated procedure to assess a predictive biomarker in the early phase of research. We believe that ERCC1 is not untypical of biomarkers being investigated for stratified medicine.
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1. Introduction

Lung cancer is one of the leading causes of cancer mortality globally [1–3]. The majority of patients have non-small-cell lung cancer (NSCLC) histology [3,4]. Prognosis in these patients is generally poor [2,4], with a five year survival of about 5% for advanced NSCLC and about 15% irrespective of stage [3]. In spite of development of new, targeted treatments, platinum-based chemotherapy remains a major part of NSCLC care [2,4–6].

The effectiveness of platinum-based chemotherapy is however limited [1,7], with resistance to treatment resulting in little or no benefit and potentially unnecessary toxicity in some patients [8].

Abbreviations: ERCC1, excision repair cross-complementation group 1; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NER, nucleotide excision repair; NR, not reported; NSCLC, non-small-cell lung cancer; PD-L1, programmed-death ligand 1; RTqPCR, reverse transcriptase quantitative polymerase chain reactio.

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In a significant number of patients, identification of biomarkers predictive of resistance to platinum-based chemotherapy could potentially result in avoiding unnecessary treatment, as well as better allocation of healthcare resources. Expression of excision repair cross-complementation group 1 (ERCC1) gene has been suggested as a biomarker potentially relevant to prediction of response to platinum-based chemotherapy [2].

The use of predictive biomarkers is becoming more common. The accuracy and replicability of the procedures used to evaluate these biomarkers (including sample collection, processing, assay, scoring system and threshold) are therefore crucial. The use of standardised procedures is important to facilitate combination of results of multiple studies in a meta-analysis and implementation of their findings in clinical practice. There are however reasons to believe that in practice there may be little consistency in these procedures. A review of published papers investigating ERCC1 expression to predict response to platinum-based chemotherapy in lung cancer found that there was large variability in the assays used [2]. This review was published in 2011, thus including relatively early ERCC1 evaluations. There was a possibility that more recent research practice has become more harmonised.

ERCC1 was also chosen as a case study, as the research investigating it as a potential predictive biomarker was relatively recent and therefore likely to illustrate current practice. An interesting development was that it was suggested that currently there may be no laboratory procedure capable of identifying the ERCC1 isoform that may be responsible for resistance to cisplatin [7].

The aim of this systematic review undertaken in 2013 and subsequent questionnaire was to investigate the consistency of methods for evaluation of ERCC1 as a biomarker predictive of response to platinum-based chemotherapy in ongoing or completed since 2007 studies in NSCLC, and to investigate the rationale for choice of a specific method. This project sets out to provide a case study of current research practice, from which lessons can be learned that may apply to a wider context of predictive biomarker research.

2. Materials and methods

Searches for studies completed since 2007 and ongoing were undertaken on 26 March 2013 in ClinicalTrials.gov, WHO and the Controlled-Trials databases. Search terms were based on the patient population (NSCLC), the biomarker (ERCC1) and treatment (platinum-based chemotherapy). The full search strategies are available in the online supplement.

Studies meeting the following criteria were included:

- Population: patients with NSCLC (any stage).
- Intervention: at least one of the study arms included platinum-based chemotherapy.
- Biomarker assay: any assay measuring ERCC1 expression or nucleotide excision repair (NER) gene expression in tumour tissue or blood.
- Outcome: any.
- Study: any ongoing study or completed/terminated after 1st January 2007.

Titles of studies were screened by two independent reviewers (KM and LB) and those clearly not meeting the inclusion criteria were excluded. For the remaining studies full records obtained from databases of ongoing trials were considered for inclusion by two independent reviewers (KM and LB). Studies were included if they met all inclusion criteria. Studies only specifying the intervention as chemotherapy or systemic therapy were also included if all the remaining criteria were met. Disagreements between reviewers were resolved by discussion and in two cases by seeking further information on the studies in internet searches.

For all included studies, information was extracted from the databases on: study phase, design, planned sample size, status (ongoing, completed, terminated or withdrawn), start and planned end date, primary outcome, patient inclusion criteria, intervention, ERCC1 evaluation, location, sponsor and contact details.

A questionnaire asking about the details of ERCC1 evaluation procedures and reasons for their choice was prepared in collaboration with clinical and pathology experts and sent to contacts for each included study, the sponsor or for published studies the corresponding author (whichever was available). The questionnaire was sent on 5th August 2013 and if no reply was received, again on 28th January 2014. For completed studies searches for publications were also undertaken.

Data obtained from databases of ongoing trials and replies received were summarised using descriptive analysis. No additional information was obtained through searches for published studies.

3. Results

3.1. Details of studies included in the systematic review

The searches identified 730 unique records in databases of clinical trials. The review process is presented in detail in Fig. 1, leading to 33 studies being included in the study.

Eighteen of the included studies were ongoing, eight completed, two terminated early and one withdrawn prior to enrolment. The status of four studies was unknown. Nine of the included studies were conducted in Asia, eight in Europe, 13 in North America, one included locations in Europe and North America and for two the location was not reported. The phase and size of studies together with design is shown in Fig. 2.

There were two key types of study design (see Fig. 2 caption for details). In 19 studies ERCC1 was not an integral part of the study design, but a correlation between the biomarker status and treatment outcome was investigated (correlative studies). The remainder used ERCC1 as an integral part of the design: thirteen used ERCC1 alone or in combination with other biomarkers to determine treatment strategy (biomarker strategy design) and one study used ERCC1 to stratify randomisation.

As expected, single arm correlative studies were most frequently early phase studies (phase 0, I and II). Nine of 15 phase II studies reported testing a strategy that was based on ERCC1 and in some cases also included other biomarkers. Phase III trials included one correlative RCT, one RCT stratified by ERCC1 and three RCTs using ERCC1 to select a treatment strategy. The phase IV study was a biomarker-based strategy RCT.

Detailed characteristics of included studies are reported in the online Supplement.

3.2. ERCC1 Information on all included studies

The procedures for evaluation of ERCC1 varied across studies (Fig. 3). Data was available in sufficient detail to enable the identification of the laboratory procedure used in 24 of the 33 studies. Of these, reverse transcriptase quantitative polymerase chain reaction (RTqPCR) was used in nine (38%) and immunohistochemistry (IHC) in five (21%) studies. Two studies reported the use of multiple methods. In one immunofluorescence-based automated quantitative analysis for in situ expression was used as the primary assay and if additional samples were available, RT-PCR, RTqPCR, polymorphism analysis and tissue microarray analysis of genes associated with DNA synthesis, damage repair, and drug efficacy

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