Tyrosine Kinase Inhibitors in Dysplasia of Lung Epithelium – a feasibility study

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Keywords: Lung Cancer; Bronchial Dysplasia; Bronchoscopy;

Word count:

Abstract

Introduction

During the pre-malignant phase in the development of squamous cell lung cancer, bronchial epithelium goes through a series of morphological changes from squamous metaplasia to low grade dysplasia and subsequently high grade dysplasia before finally transforming to invasive carcinoma. Dysplasia is a field change effect and while central airways disease may be treated with endobronchial therapies such as photodynamic therapy or electrocautery, dysplastic change may occur in airways beyond bronchoscopic range. Therefore a systemic treatment may have greater efficacy.

Three objectives were identified for a programme of research: (i) to identify people at high risk of lung cancer by virtue of harbouring pre-malignant lesions in their lung; (ii) to monitor pre-malignant lesions for signs of progression to malignancy using minimally invasive techniques; and (iii) to treat high-grade lesions before they pose a risk to the patient. The first step in this programme was to identify a group of potential study entrants. The TIDAL1 feasibility study was designed to determine, in patients at high risk of lung dysplasia who are screened with auto-fluorescent bronchoscopy, whether the incidence of high-grade dysplasia is sufficient to make further steps in the planned research programme a feasible endeavour.

The study also aimed to provide an early indication as to whether the EGFR inhibitor gefitinib can resolve the dysplastic process. The development of dysplasia is characterised by EGFR overexpression (Merrick et al., Clin Cancer Res 2006;12(7)). Gefitinib (ZD1839, Gefitinib, AstraZeneca Pharmaceuticals, Wilmington, Del.) is an oral inhibitor of EGFR tyrosine kinases. There are extensive *in vitro* and *in vivo* data demonstrating that Gefitinib blocks proliferation in cell culture induced by activation of EGFR and causes regression of human tumour xenografts with EGFR over-expression. If such a signal was demonstrated then future randomized trials of EGFR inhibition in this setting would be warranted. This paper reports the results from the TIDAL1 study.

MATERIALS AND METHODS

Study design

TIDAL1 was a single arm cohort feasibility study involving a two-stage consent process. The first stage of the study screened participants for high-grade dysplasia and the second stage treated those found to harbour high-grade dysplasia. The study was sponsored by and undertaken at Royal Papworth Hospital NHS Foundation Trust and co-ordinated by Papworth Trials Unit Collaboration. The protocol received ethics approval from the East of England Cambridge East Research Ethics Committee (11/H0304/8) and was registered with the Medicines and Healthcare products Regulatory Agency (MHRA) on 18th May 2011 and on clinicaltrials.gov (NCT01405).

Participants and interventions

Patients who had undergone either surgical resection for non small cell lung cancer (NSCLC) or treatment with curative intent for squamous cell head and neck cancer at least three months previously were deemed to be at high risk of dysplasia and therefore eligible for the study. Participants had to be aged ≥ 18 years, Eastern Cooperative Oncology Group performance status of 0 or 1, suitable for flexible bronchoscopy, able to give informed consent and meet pre-determined haematological, renal and liver function parameters. For stage 1, patients meeting all inclusion and no exclusion criteria (see on-line supplementary information for details) underwent a contrast-enhanced staging CT of chest and abdomen and if this did not show any evidence of new or recurrent malignant disease or interstitial lung disease, a flexible bronchoscopy with autofluorescence was performed (see on-line supplementary information for protocol). Patients found at bronchoscopy to have areas of high-grade dysplasia (severe dysplasia or carcinoma in situ) were consented to stage 2 of the study as long as they continued to meet all inclusion and no exclusion criteria. Patients progressing to stage 2 received gefitinib 250 mg as an oral tablet daily for 26 weeks. Assessment at 2, 4, 12 and 26 weeks after the start of treatment included physical examination, haematological, renal and liver function, toxicity assessment by Common Toxicity Criteria (CTC) scoring, documentation of adverse events, assessment of compliance with medication (pill count) and

concomitant medication recording. At 26 weeks chest radiography, assessment of smoking status and repeat flexible bronchoscopy with autofluorescence was also undertaken. Response of high-grade dysplasia to treatment compared with baseline was made using photography and re-biopsy of each lesion. Criteria used to determine treatment response (complete or partial response, stable or progressive disease) are listed in on-line supplementary Appendix X. If there was any evidence of progression to invasive disease, study participation was discontinued and the patient managed by the clinical team. In the absence of invasive disease a further chest radiograph and bronchoscopy with autofluorescence was undertaken at 52 weeks after commencement of gefitinib.

Primary and secondary outcomes

The primary outcome measure of the study was the incidence of high-grade dysplasia of the bronchial epithelium diagnosed through autofluorescence bronchoscopy in patients at high risk of bronchial dysplasia. Dysplasia is assessed by photography and histology and graded as low, moderate or high. Secondary outcome measures include patient acceptability of study procedures and treatment indicated by willingness to participate in the study and successful biobanking of bronchial biopsies for molecular characterization. Other secondary outcome measures relating to treatment include response of high-grade dysplasia to treatment and toxicity of treatment as assessed by CTC toxicity scoring. .

Statistical Analysis

The primary aim of this study was to estimate the proportion of patients in the risk population who are diagnosed as having high-grade dysplasia of the bronchial epithelium on autofluorescence bronchoscopy. There was little information on the true value of this proportion and the aim of this study was to reduce this uncertainty. The statistical analysis is a likelihood-based Bayesian approach to estimation of the proportion using a Beta-Binomial conjugate analysis with a minimally informative Beta(1,1) prior. The analysis will estimate a posterior probability distribution with 80% and 95% credible intervals and estimate the

probability that the true proportion is less than 10% which is the level at which further research of this condition in this population would be deemed infeasible.

The target sample size for the study was 40 patients from the risk population. With this number of patients and a minimally informative Beta (1,1) prior distribution the posterior Beta probability distribution for the estimate would have at most a standard deviation of 0.0762 (with an observed proportion of 50%) and this will give 80% and 95% credible intervals of width 0.2 and 0.3 respectively. It was deemed that this would give sufficient precision in the estimate to assess feasibility and inform the next phase of the research. In addition, it was estimated that 10 of these 40 patients would be eligible to receive gefitinib.

All secondary outcome measures are reported using a purely descriptive approach. Acceptability will be reported as the proportion of eligible patients who consent to participation and biobanking success will be reported as the proportion of planned biopsies that were collected and stored such that they are usable for histopathological assessment. Response will be reported as the number of participating patients falling into each category and any adverse events experienced will be described.

Post treatment on-going management

Following completion of the study period, on-going management was at the discretion of the managing clinician. No restriction was placed on any subsequent treatment.

Role of the funding source

The study sponsor (Royal Papworth Hospital NHS Foundation Trust) and study funder (Noble Foundation) had no access to the dataset and did not influence the design, analysis or reporting of the study. All authors had access to the data and the decision to submit for publication was made solely by the authors.

RESULTS

Between December 2011 and February 2016, 200 patients were assessed for eligibility (see Figure 1). One hundred and fifty two were excluded for not meeting inclusion criteria (n=99), declining to participate (n=28) or because either they wanted their long-term follow up in a local hospital (n=13) or because the managing clinician did not feel the study appropriate for the patient (n=12). At the time of trial closure, a further 14 patients had been identified but not yet approached and 2 had been approached but had not been consented to part 1 screening investigations.

Of the 32 patients who consented to screening investigations, 23 proceeded to bronchoscopy. Seven patients failed screening criteria and did not proceed to bronchoscopy and two patients were pending screening investigations at the time of study closure. Of the 23 patients who underwent bronchoscopy, 2 patients were found to have high-grade dysplasia, 6 low-grade dysplasia and 15 no dysplasia. Given these data and the minimally informative prior probability distribution, the Bayesian posterior probability distribution for the true incidence rate of high dysplasia (Figure 2) had mean of 12% and median of 11%. Credible intervals showed that there is a 95% chance that the true incidence rate falls between 2.7% to 27.0% and 80% chance that it falls between 4.7% and 20.7%. The posterior distribution shows there is a 56% chance that the incidence rate is greater than 10%.

Both patients with high-grade dysplasia (at the bronchial resection margin) consented to the second stage of the study and received 6 months treatment with gefitinib. One patient was found to have no dysplasia at the 26 week bronchoscopy and low grade dysplasia at 52 weeks while the other patient had persistence of high grade dysplasia at 26 and 52 weeks.

DISCUSSION

REFERENCES

Merrick et al., Clin Cancer Res 2006;12(7)

FIGURES

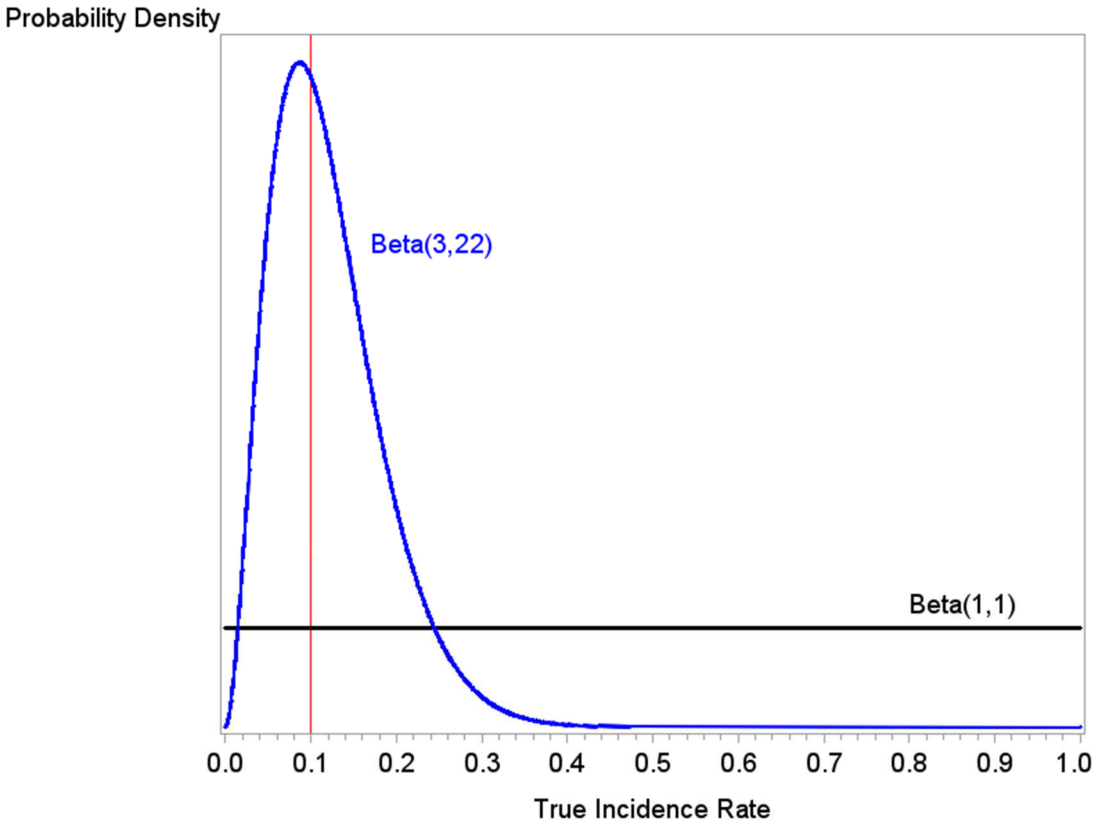
Figure 1

TIDAL 1 consort diagram

Figure 2

Bayesian posterior probability distribution for the true incidence rate of high grade dysplasia (blue curve), prior probability distribution (black line) and critical value (red line)

Figure 2


Probability Density
Beta(3,22)
Beta(1,1)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
True Incidence Rate