

Gefitinib in the adjuvant setting: safety results from a phase III study in patients with completely resected non-small cell lung cancer

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Standard therapy for stage I–IIIA non-small cell lung cancer (NSCLC) is surgery, although adjuvant therapies are required to prevent disease recurrence and improve patient survival. This is the first study that planned to administer adjuvant gefitinib (Iressa) 250 mg/day or placebo to randomized patients with completely resected NSCLC (stage IB–IIIA) 4–6 weeks following surgery, for 2 years, until recurrence/withdrawal. However, recruitment was stopped after the randomization of 38 patients, because interstitial lung disease (ILD)-type events were being increasingly reported in Japan in the advanced disease setting. Finally, the trial was halted. Safety data for 38 recruited patients (18 gefitinib and 20 placebo) showed no unexpected adverse drug reactions (ADRs), with the most common being grade 1/2 gastrointestinal and skin disorders in 12 and 16 patients receiving gefitinib and in five and six patients receiving placebo, respectively. Grade 3/4 ADRs occurred in four patients receiving gefitinib and one patient receiving placebo. ILD-type events were reported in one patient receiving gefitinib (concomitantly with other ILD-inducing drugs) who died and two patients receiving placebo. Eight patients receiving gefitinib withdrew due to ADRs compared with three patients receiving placebo. Adverse events associated with surgical complications were reported for six patients receiving

gefitinib and four patients receiving placebo. In the adjuvant setting there were no unexpected adverse events observed. Gefitinib had no impact on surgery-related complications when given within 4–6 weeks post-operatively. *Anti-Cancer Drugs* 16:1123–1128 © 2005 Lippincott Williams & Wilkins.

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Sponsorship: This trial was coordinated and supervised by the Study Coordinating Committee (principal investigators plus AstraZeneca personnel), and the Independent Data Monitoring Committee (lung cancer and statistical experts independent of AstraZeneca), with funding and organizational support from the trial sponsor AstraZeneca.

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Introduction

Non-small cell lung cancer (NSCLC) is generally not diagnosed until the disease is symptomatic, by which time more than two-thirds of patients are in the advanced stages of disease and have a poor prognosis [1]. Approximately 25% of patients with NSCLC are diagnosed when their disease is in the early stages; however, as many of these patients frequently have undetectable metastases, disease often recurs in distant sites [2]. Adjuvant therapies are therefore required to help prevent disease recurrence and as they will need to be given to patients post-operatively for a prolonged period, they should be well tolerated.

Although some clinical trials in NSCLC have shown a significant survival benefit with adjuvant uracil plus tegafur (UFT) and cisplatin-based chemotherapy [3–7], others have not observed a significant improvement in

survival [5,8,9]. At the time of commencing this study, there were no standard adjuvant treatment regimens for NSCLC.

Gefitinib (Iressa), an orally active epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), was approved in Japan for the treatment of inoperable or recurrent NSCLC in 2002. Two large phase II trials, IDEAL (Iressa Dose Evaluation in Advanced Lung cancer) 1 and 2, observed objective responses and stable disease in more than 40% of pre-treated patients with NSCLC receiving 250 mg/day gefitinib, with the majority of adverse events (AEs) being mild to moderate gastrointestinal and skin disorders [10,11]. Gefitinib was not associated with the well-recognized AEs observed with cytotoxic chemotherapy (e.g. bone marrow depression, neurotoxicity, nephrotoxicity). The tolerability profile of gefitinib has been confirmed by data from the

Expanded Access Programme, through which more than 39 000 patients have received gefitinib 250 mg/day on a compassionate-use basis. Furthermore, a retrospective analysis of 9515 US patients who had received gefitinib for 1 year or more via the Expanded Access Programme showed a 1-year survival rate of 33% [12], which compares with the IDEAL studies [10,11]. Recently, Onn *et al.* observed efficacy (16% with objective responses and 45% with stable disease) and a low incidence of grade 3/4 AEs in Japanese patients with NSCLC, most of whom had been treated with second-line gefitinib or above (99% of patients) [13].

To date, there is no experience of using gefitinib in the post-operative adjuvant setting. This phase III trial was initially undertaken to compare survival rates in patients with completely resected stage IB–IIIA NSCLC who had been treated with adjuvant gefitinib 250 mg/day or placebo. However, in October 2002, recruitment was halted following high-profile media activity around reports of gefitinib-related interstitial lung disease (ILD)-type events in patients with advanced or meta-static NSCLC in Japan. In March 2003, the trial was halted because of an increased withdrawal rate. As enrollment could not be resumed until the prospective investigation into gefitinib-related ILD-type events in Japan was completed, the trial was closed. Consequently survival data are not available, although data from patients recruited to the study have been subsequently analyzed for safety.

Methods

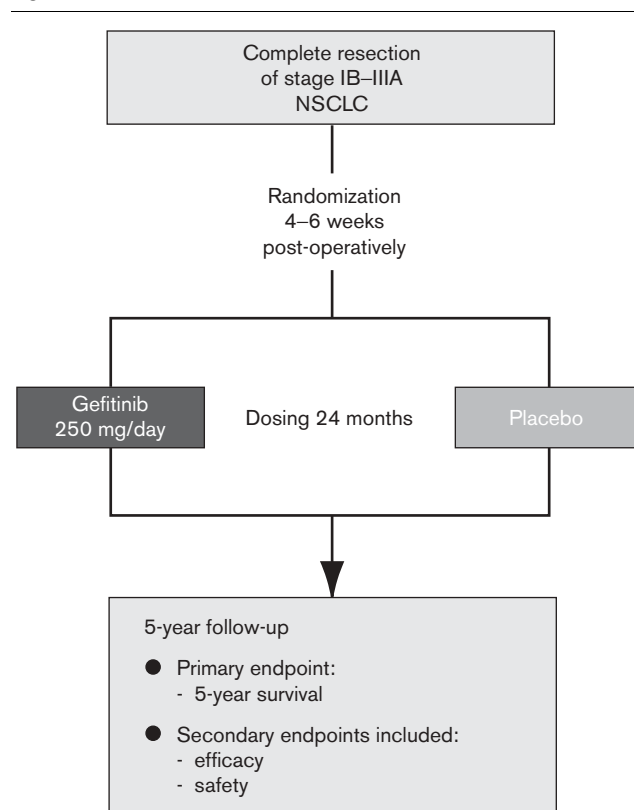
Patients

Patients were eligible for inclusion in the trial if they had histologically confirmed NSCLC (post-operative stage IB–IIIA) that had been completely resected 4–6 weeks before the start of treatment. Patients were required to be 20–75 years of age, with a WHO performance status (PS) 0–1, no previous history of chemotherapy, radiotherapy or immunotherapy for NSCLC and no co-malignancies within the past 5 years. All patients gave written, informed consent to participate in the trial, which was conducted in accordance with the Declaration of Helsinki [14] and Good Clinical Practice guidelines.

Study design

This randomized (1:1), double-blind, placebo-controlled, phase III multicenter survival study planned to recruit 670 patients (335 per group) and randomize them to receive either gefitinib (250 mg) or placebo (Fig. 1). Treatment was to be continued for 2 years, or until recurrence/secondary carcinoma or withdrawal criteria were met. An Independent Data Monitoring Committee (IDMC) was set up to assess the efficacy and safety of gefitinib post-operatively, and would advise whether the study should be continued, changed or discontinued.

Fig. 1



Trial design schema.

Assessments

Efficacy

Disease recurrence or secondary carcinogenesis were assessed using X-rays every 3 months during treatment and every 6 months during the follow-up period. Computed tomography (CT) scans were carried out 8 weeks after the first dose (where necessary, the pre-operative thoracoabdominal CT scan could be used), at week 48 during treatment, at week 104 after withdrawal/completion and every 52 weeks thereafter, unless disease recurrence was observed.

Safety

AEs were to be recorded and coded using MedDRA (Medical Dictionary for Regulatory Activities) version 6.0, graded using National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 and assigned causality by the investigators. AEs associated with post-operative complications were defined as events occurring within 90 days after surgery and were recorded without regard to causality. Treatment could be interrupted for up to 14 days, although the IDMC later recommended that drug interruption could be allowed for more than 14 days in cases where ILD-type events were suspected, but could not be confirmed, in order to ensure the safety of

patients who remained in the trial after recruitment was halted. Hematology, biochemistry and urinalysis were also measured at baseline and during the study.

Role of the funding source

This trial was coordinated and supervised by the principal investigators, the IDMC and AstraZeneca personnel, with funding and organizational support from the trial sponsor AstraZeneca.

Results

Patients

Between August and October 2002, 38 patients were randomized into the trial – 18 received gefitinib and 20 received placebo. Patient demography was well balanced between the treatment arms, with the majority of patients having adenocarcinoma histology and WHO PS 1 (Table 1). When the trial was stopped, four patients in the gefitinib arm and 11 patients in the placebo arm were

still receiving treatment (Fig. 2). Of the 23 patients who withdrew, 13 did so because of AEs (10 in the gefitinib arm and three in the placebo arm), five were unwilling to continue with treatment (three in the gefitinib arm and two in the placebo arm), two had disease recurrence (both in the placebo arm) and three withdrew for other reasons (one patient in the gefitinib arm had incomplete recovery from surgery that was not drug related, and two patients in the placebo arm had pre-existing interstitial pneumonia and were withdrawn at the request of the sponsor).

Efficacy

From the limited efficacy data, disease recurrence was not seen in patients receiving gefitinib at data cutoff. Three patients who received placebo (one with stage IB and two with stage IIB) experienced disease recurrence – two patients recurred during the trial and one patient recurred after the trial had stopped.

ADRs

No unexpected ADRs were observed and, in general, the frequency of all ADRs was higher for gefitinib versus placebo (Table 2). The most common ADRs were mild to moderate grade 1/2 gastrointestinal and skin disorders. Grade 3/4 ADRs were seen in four patients in the gefitinib arm and one patient in the placebo arm (Table 3), all of whom had treatment withdrawn (the patient with grade 3 eczema had treatment withdrawn due to grade 2 impetigo).

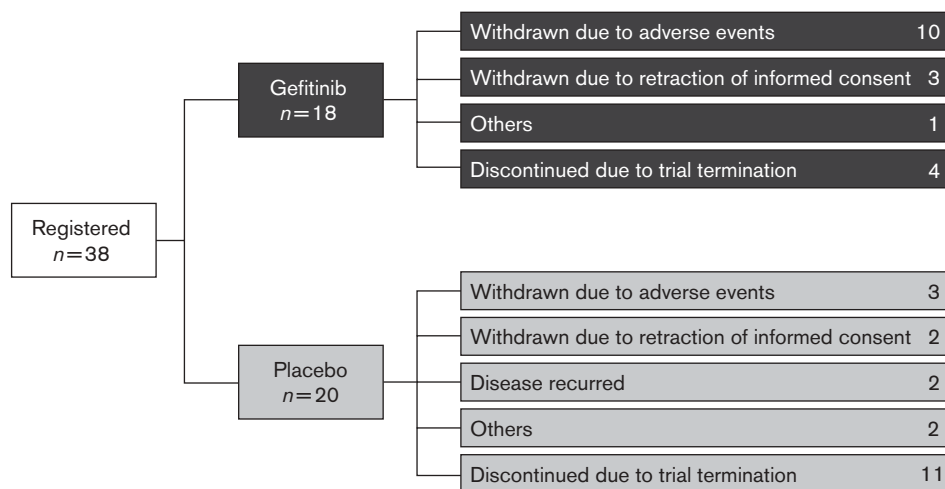
Respiratory ADRs

The majority of respiratory ADRs were grade 1/2 and occurred within 1 month of treatment. In the gefitinib arm, two patients experienced cough (associated with post-operative complications), one patient had dyspnea,

Table 1 Patient demography

	Gefitinib 250 mg/day (n=18)	Placebo (n=20)
Sex [n (%)]		
male	14 (77.8)	15 (75.0)
female	4 (22.2)	5 (25.0)
Median age [years (range)]	64.0 (49–73)	62.5 (52–73)
WHO PS [n (%)]		
0	5 (27.8)	9 (45.0)
1	13 (72.2)	11 (55.0)
Histology [n (%)]		
squamous cell carcinoma	4 (22.2)	6 (30.0)
adenocarcinoma	14 (77.8)	14 (70.0)
Stage [n (%)]		
IB	7 (38.9)	8 (40.0)
IIA	2 (11.1)	1 (5.0)
IIB	3 (16.7)	5 (25.0)
IIIA	6 (33.3)	6 (30.0)

Fig. 2



Trial outcome.

Table 2 Common ADRs occurring in two or more patients

AE (MedDRA term) ^a	Gefitinib 250 mg/day (n=18)	Placebo (n=20)
Abnormal hepatic function	4	0
Acne	2	0
Anorexia	5	1
Cough	2 ^b	1
Diarrhea	9	2
Dry skin	3	0
Eczema	8	2
Elevated ALT/AST	2	0
Fatigue	2	0
Gastritis	3 ^b	0
Loose stools	4	0
Nausea	3	0
Rash	5	3
Sputum	0	2
Stomatitis	2	0

^aA patient could have more than one AE.^bAll were associated with post-operative complications.**Table 3 Grade 3/4 ADRs**

AE (MedDRA term)	Grade	Gefitinib 250 mg/day (n=18)	Placebo (n=20)
Abnormal hepatic function	3	1	0
Eczema	3	1	0
Elevated ALT	3	1	0
Neutropenia	3	0	1
Pneumonitis	4	1	0

and one patient experienced grade 4 ILD-type events (pneumonitis) 107 days after starting gefitinib and was withdrawn from the study. The patient with pneumonitis had taken concomitant shosaikoto, a Chinese herbal medicine, and loxoprofen, both of which have previously been shown to induce pneumonitis [15,16]. Twenty-one days later bacterial pneumonia related to methylprednisolone therapy was diagnosed, and the patient subsequently died 37 days later due to both pneumonitis and bacterial pneumonia. In the placebo arm, one patient who experienced cough and grade 1 pulmonary fibrosis had had interstitial changes on their chest X-ray at enrollment, and in a second patient, pre-existing non-specific interstitial pneumonia was exacerbated resulting in grade 1 ILD. In both patients, these conditions persisted following withdrawal of study drug.

Interruptions and withdrawals due to ADRs

ADRs requiring interruptions in therapy were similar between patients receiving gefitinib or placebo (Table 4) and were usually for less than 14 days, although four patients in the gefitinib arm required treatment to be interrupted for 14 days (including one patient whose treatment was interrupted for 20 days). The majority of ADRs leading to withdrawal were usually mild-to-moderate grade 1/2 in severity (Table 5). Grade 3 ADRs leading to withdrawal occurred in two patients receiving gefitinib (hepatic function abnormalities, elevated ALT)

Table 4 Exposure of patients to gefitinib

	Gefitinib 250 mg/day (n=18)	Placebo (n=20)
Median duration of treatment [days (range)]	86.5 (4–195)	144.0 (20–197)
Dosing period (n)		
< 60 days	6	2
60–120 days	9	4
≥ 120 days	3	14
No. dose interruptions (n)		
1	5	6
2	2	2
≥ 3	2	2

Table 5 ADRs leading to patient withdrawals

Adverse event (MedDRA term)	Grade	Gefitinib 250 mg/day (n=18)	Placebo (n=20)
Eczema	2	1	0
Elevated ALT/AST	2	1	0
	3	1	0
Hepatic function abnormalities	2	1	0
	3	1	0
ILD	1	0	1
Impetigo	2	1	0
Neutropenia	3	0	1
Paronychia	2	1	0
Pneumonitis	4	1	0
Pulmonary fibrosis	1	0	1

and in one patient receiving placebo (neutropenia), and grade 4 pneumonitis led to the withdrawal of one patient who was receiving gefitinib. Following withdrawal of gefitinib treatment, grade 3 abnormal hepatic function and elevated ALT resolved, and grade 3 neutropenia persisted.

AEs associated with post-operative complications

As there are no safety data regarding the use of gefitinib in the post-operative setting, AEs associated with the healing process were examined to provide preliminary safety data on the start of the dosing timing in the adjuvant setting for gefitinib. AEs related to post-operative complications were observed in six patients in the gefitinib arm and four patients in the placebo arm. In the gefitinib arm, the most frequent AEs were grade 1/2 cough (four patients) and gastritis (three patients), and in the placebo arm grade 1/2 pain (three patients). Grade 1 cough, grade 1 supraventricular arrhythmia and grade 2 dyspnea were also experienced by three out of four patients receiving placebo.

Discussion

This trial was designed to compare survival rates in patients with completely resected stage IB–IIIA NSCLC who had received adjuvant therapy with gefitinib 250 mg/day or placebo. However, incidences of ADRs of ILD-

type events in the advanced disease setting have been increasingly reported since gefitinib was launched in Japan, and new recruitment was put on hold on 23 October 2002 at the request of the Ministry of Health, Labor and Welfare. In order to evaluate the ILD and ensure the safety of the trial patients, two separate Co-ordination Committee and IDMC meetings (December 2002 and January 2003) were conducted to discuss the feasibility of continuing the study and management of the trial patients. Based on the updated information on ADRs of interstitial pneumonia, the committees concluded that the study could be continued because the possibility of risk did not exceed that of benefit to enrolled patients. The IDMC also suggested that top priority should be given to assure the safety of the patients receiving gefitinib, and that discontinuation should be considered if flu-like symptoms including difficulty in breathing, fever and coughing occurred.

A 'Supplemental Explanation Sheet and Informed Consent Form' was provided four times to enrolled patients, offered updated information and methods to assure and manage any safety issues, and confirmed the patients' willingness to continue participating in the study. In December 2002, AstraZeneca KK gave the principal investigators the option to suspend gefitinib treatment at once. With the extensive monitoring of the trial patients in terms of safety, there were still an increasing number of withdrawals. In addition, enrollment could not be resumed until the prospective investigation on gefitinib-related ILD was completed. Based on these facts, the sponsor finally decided to terminate the trial in March 2003.

The types of AEs reported in this trial were similar to that already reported in the large phase II IDEAL 1 and 2 trials for patients with locally advanced or metastatic NSCLC [10,11]. Three patients experienced ILD-type events – two in the placebo arm and one patient in the gefitinib arm (this patient was also taking two other medications known to induce ILD) [15,17]. It has generally been observed that a higher frequency of ILD-type events are reported in Japanese patients taking gefitinib compared with those in other south-east Asian countries and the rest of the world (1.6, 0.3, and 0.3%, respectively) [18]. The occurrence of ILD in Japanese patients and the reasons for such an ethnic stratification in ILD incidence following gefitinib treatment require further clarification.

The most common reason for withdrawal in both treatment arms was due to toxicity, with the majority of drug-related AEs being grade 1/2 in severity. In the advanced or metastatic disease setting, few patients who experience grade 1/2 drug-related AEs withdraw from treatment with gefitinib, and in IDEAL 1, which

recruited Japanese patients, two out of 103 patients who received gefitinib 250 mg/day withdrew from therapy due to ADRs [18]. Several factors may explain the high number of withdrawals (including withdrawal of treatment for less severe ADRs) reported in this trial data compared with previously reported studies. These reasons include the fact that patients with early-stage NSCLC may be less tolerant of AEs compared with patients with advanced NSCLC who have received prior chemotherapy. In contrast to the other studies, the impact of heavy media coverage surrounding gefitinib-related ILD cannot be ignored.

It has been suggested that the dosage and schedule of gefitinib used in this study may not best suit patients with completely resected NSCLC in terms of tolerability and a number of adjustments may need to be taken into consideration when planning an adjuvant study of gefitinib in the future. It is unlikely that the time frame of 4–6 weeks is too short before starting adjuvant treatment, as other adjuvant trials conducted in Japanese patients have used similar time frames [3,4]. It may be possible to lengthen the duration by which gefitinib could be interrupted for toxicity, since 14 days may be too short for patients recovering from AEs such as hepatic enzyme elevation, or to reduce the dose following toxicity to perhaps 250 mg every other day, although this would require further study into the efficacy of such an approach.

With no experience of using gefitinib in post-operative patients there was a concern that EGFR-TKIs might impact on surgery-related complications (especially on the healing process) due to their mode of action. In order to assess this, the trial was designed to allow a safety review of the first 60 patients. Due to the early termination of the study, we have only 38 patients' (18 on gefitinib) data for review; however, there does not seem to be any impact on surgery-related complications when gefitinib was administered within 4–6 weeks after surgery, as evidenced by a similar number of these AEs that occurred in both groups. This indicates that it may be feasible to administer gefitinib in the adjuvant setting within this time frame.

In conclusion, this is the first study to investigate the use of EGFR-TKIs as adjuvant therapy. Despite the absence of survival data, there were no unexpected AEs seen in the adjuvant setting compared with those already reported for patients with locally advanced or metastatic NSCLC. However, it was observed that there were more AEs leading to withdrawal in the gefitinib arm, even though the majority of AEs were grade 1/2 in severity, suggesting that a daily dose of gefitinib 250 mg may not best suit patients with completely resected NSCLC in terms of tolerability.

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