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Overview of the Tolerability of Gefitinib (IRESSA™) Monotherapy

Clinical Experience in Non-Small-Cell Lung Cancer

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Contents

Abstract

Cytotoxic chemotherapy treatment options for patients with non-small-cell lung cancer (NSCLC) have limited efficacy and are often associated with significant toxicity. Therefore, there is an unmet need for novel drugs that are not only effective in treating this disease but are also well tolerated. Gefitinib is an orally active epidermal growth factor receptor tyrosine kinase inhibitor that blocks the signal transduction pathways implicated in cancer cell growth and survival. It has recently been approved for the treatment of advanced/refractory NSCLC. This review presents the tolerability data from phase I and II gefitinib monotherapy trials, along with data from the worldwide 'Expanded Access Programme' and post-marketing use of gefitinib.

Gefitinib was found to be generally well tolerated at the approved dosage of 250 mg/day; the most commonly reported adverse drug reactions (ADRs) were mild to moderate skin rash and diarrhoea, which were manageable and non-cumulative. Other ADRs observed with the use of gefitinib included: dry skin, pruritus, acne, nausea, vomiting, anorexia, asthenia and asymptomatic elevations in liver transaminase levels. Well recognised adverse effects seen with cytotoxic chemotherapy (such as bone marrow depression, neurotoxicity and nephrotoxicity) were not observed. Although the frequency and severity of ADRs increased with the dosage across the range studied (50–1000 mg/day), few patients required dosage reductions or the withdrawal of treatment, and those who did usually received gefitinib ≥600 mg/day.

Thus, the available data indicate that gefitinib is well tolerated in patients with a range of solid tumours, including locally advanced or metastatic NSCLC.

Lung cancer, of which non-small-cell lung cancer (NSCLC) accounts for 80% of cases worldwide, is generally not diagnosed until the disease is symptomatic, by which time it is often in the advanced stages.[1] Current treatment options for patients with locally advanced or metastatic NSCLC combine standard platinum-based chemotherapy agents, such as cisplatin and carboplatin, with newer agents, such as the taxanes, gemcitabine and vinorelbine, thereby increasing response rates and prolonging survival.[2-4] However, clinical benefit does not depend on the chemotherapy regimen used, as response rates (19%) and 1-year survival rates (33%) in chemonaive patients with advanced NSCLC were found to be comparable in a study evaluating four different chemotherapy regimens (cisplatin plus paclitaxel or gemcitabine or docetaxel, and carboplatin plus paclitaxel).[5] For patients in whom the disease relapses following platinum therapy, two chemotherapy agents are approved, docetaxel (response rates of 4–9% and a 1-year survival rate of 30–37%)[6-8] and pemetrexed, which was recently approved in the US for second-line chemotherapy (response rate of 9% and 1-year survival rate of 30%).[8] For patients who relapse following platinum- and docetaxel-based chemotherapy, the major aim is palliation and it is important that the benefit of treatment is not overshadowed by safety concerns. Indeed, many patients may choose best supportive care rather than experience the toxicity associated with cytotoxic chemotherapy (which can include haematological and biochemistry changes, severe nausea and vomiting, and alopecia).[9] Therefore, there is an unmet need for novel drugs that are not only effective but also well tolerated in patients with locally advanced or metastatic NSCLC.

Molecular targets for anticancer drugs include the epidermal growth factor receptor (EGFR). A wide variety of tumours express the EGFR[10] and EGFR tyrosine kinase activation is important in the growth and survival of many solid tumours.[11] Gefitinib (IRESSA™)[1] is an orally active anilinoquinazoline that blocks EGFR tyrosine kinase autophosphorylation and signal transduction, thereby preventing cancer cell growth and survival.[12] Gefitinib has been extensively investigated and is the first EGFR tyrosine kinase inhibitor to be approved for the treatment of advanced/refractory NSCLC.

This article reviews the safety and tolerability data from phase I and II gefitinib monotherapy trials, with particular emphasis on data from pretreated patients with NSCLC. Supportive data from subsequent clinical studies, from an extensive 'Expanded Access Programme' (EAP) that provided gefitinib to patients with NSCLC for whom no other treatment options existed, and from post-marketing use of gefitinib are also included.

1. Methodology

Patients who were recruited into the phase I and II gefitinib monotherapy trials had locally advanced or metastatic cancer with significant comorbidity. At each patient visit, any adverse events experienced were recorded, coded using COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms) and graded from 1 to 4 using National Cancer Institute Common Toxicity Criteria (CTC) version 2.0.[13] These adverse events were then assigned possible causality to the study treatment by the investigators, being either a gefitinib-related adverse drug reaction (ADR) or not. The safety profile of gefitinib was further assessed by routine monitoring of laboratory values (including haematology, and renal and hepatic function). Where necessary, ADRs were managed by providing a brief therapy interruption (up to 14 days) or by reducing the dosage of gefitinib if they did not resolve either spontaneously or following medical intervention.

Prior to approval in over 30 countries (including the US, Canada, Japan, Switzerland and Australia), the EAP provided the largest exposure to gefitinib (at a dosage of 250 mg/day in patients with advanced, inoperable NSCLC. Serious ADRs from clinical trials, the EAP and post-marketing use are reported to AstraZeneca's Drug Safety division. Ongoing safety surveillance activities are conduct-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

ed, including a regular review of the Global Drug Safety database to identify and evaluate any issues that may affect patient safety. Serious ADRs are followed up with the reporter (when necessary) to obtain more information on individual cases and ensure that events are being documented as accurately as possible.

Consistent with the EGF-dependent nature of normal ocular homeostasis,[14] preclinical data suggested that gefitinib may cause ophthalmological ADRs (reversible thinning of the corneal epithelium and non-reversible corneal opacification).[15] Consequently, stringent ophthalmological monitoring (visual acuity, slit-lamp examinations, lid eversion and Schirmer's test) was performed in these phase I trials. Non-clinical data also suggested that gefitinib may affect cardiac action potential[16] and therefore serial ECGs were undertaken.

2. Phase I Clinical Trials

The tolerability of gefitinib in patients with a wide range of solid tumours, including 106 patients with NSCLC, has been investigated in five multiple-dosage, phase I, multicentre trials. In two of these trials, increasing dosages of gefitinib (50–700 mg/day) were administered orally for 14 days, followed by 14 days of observation per 28-day treatment period.[17,18] The other three trials used dosages of 150–1000 mg/day for 28 days per 28-day treatment period.[19-21] The number of patients given each dosage is summarised in table I. For simplicity, the dosages have been grouped as follows: <225 mg/day (50, 100 and 150 mg/day); ~250 mg/day (225 and 300 mg/day); ~500 mg/day (400, 500 and 525 mg/day); and >525 mg/day (600, 700, 800 and 1000 mg/day).

In all five trials, the majority of patients had received prior chemotherapy (94.4%), had a WHO performance status of 1 (restricted but ambulatory) [67.0%] and were <65 years of age (74.4%). A total of 270 patients were exposed to gefitinib (table II); the maximum duration of treatment was observed in patients who received ~250 mg/day and the mean duration of treatment in these patients was 77 days.

Table I. Number of patients receiving each dosage of gefitinib in the phase I trials

Gefitinib dosage (mg/day)	Dose scheduling	
	14 days[a] (n = 95)	28 days[b] (n = 175)
50	13	
100	11	
150	8	19
225	13	27
300	8	27
400	11	27
500		18
525	16	
600		20
700	15	
800		20
1000		17

a Patients received gefitinib daily for the first 14 days of each 28-day treatment period.

b Patients received gefitinib daily.

Overall, gefitinib was well tolerated in all patients. The most common ADRs were diarrhoea (43.3%), skin rash (40.7%), acne (20.0%), dry skin (18.9%), nausea (15.6%), pruritus (10.7%), vomiting (10.4%), asthenia (8.5%) and asymptomatic elevations in liver transaminase levels (5.6% for alanine aminotransferase [ALT] and 6.3% for aspartate aminotransferase [AST]), with the majority being mild to moderate CTC grade 1 or 2 (table III). Well-recognised adverse effects seen with cytotoxic chemotherapy (such as bone marrow depression,

Table II. Exposure of patients with a range of solid tumours to gefitinib in phase I multiple-dosage trials

Exposure parameter	Gefitinib dosage (mg/day)			
	<225 (n = 51)	~250[a] (n = 75)	~500[b] (n = 72)	>525 (n = 72)
No. of dosing days				
Total	2356	5776	3883	4780
Mean	46.2	77.0	53.9	66.4
Range	1–458	1–506	7–404	5–395
Months receiving treatment [n (%)]				
<1	38 (74.5)	31 (41.3)	41 (56.9)	34 (47.2)
1–3	10 (19.6)	28 (37.3)	19 (26.4)	22 (30.6)
>3–6	1 (2.0)	8 (10.7)	9 (12.5)	10 (13.9)
>6	2 (3.9)	8 (10.7)	3 (4.2)	6 (8.3)

a 225 and 300 mg/day, inclusive.

b 400, 500 and 525 mg/day, inclusive.

Table III. Patients (percentage) experiencing an adverse drug reaction with an overall incidence of ≥5% in phase I multiple-dosage trials

Adverse events by body system [n (%)][a]	Gefitinib dosage (mg/day)				
	<225 (n = 51)	~250[b] (n = 75)	~500[c] (n = 72)	>525 (n = 72)	All dosages (n = 270)
Digestive					
Diarrhoea	6 (11.8)	24 (32.0)	31 (43.1)	56 (77.8)	117 (43.3)
Nausea	1 (2.0)	7 (9.3)	12 (16.7)	22 (30.6)	42 (15.6)
Vomiting	2 (3.9)	4 (5.3)	5 (6.9)	17 (23.6)	28 (10.4)
Dry mouth	2 (3.9)	4 (5.3)	2 (2.8)	15 (20.8)	23 (8.5)
Anorexia	1 (2.0)	2 (2.7)	5 (6.9)	11 (15.3)	19 (7.0)
Metabolic and nutritional					
AST increased	1 (2.0)	4 (5.3)	7 (9.7)	5 (6.9)	17 (6.3)
ALT increased	1 (2.0)	4 (5.3)	5 (6.9)	5 (6.9)	15 (5.6)
Skin and appendages					
Rash	8 (15.7)	23 (30.7)	34 (47.2)	45 (62.5)	110 (40.7)
Acne	4 (7.8)	15 (20.0)	18 (25.0)	17 (23.6)	54 (20.0)
Dry skin	1 (2.0)	12 (16.0)	16 (22.2)	22 (30.6)	51 (18.9)
Pruritus	2 (3.9)	3 (4.0)	9 (12.5)	15 (20.8)	29 (10.7)
Whole body					
Asthenia	1 (2.0)	5 (6.7)	6 (8.3)	11 (15.3)	23 (8.5)

a Patients may have had more than one adverse event.

b 225 and 300 mg/day, inclusive.

c 400, 500 and 525 mg/day, inclusive.

ALT = alanine aminotransferase; **AST** = aspartate aminotransferase.

neurotoxicity and nephrotoxicity) were not observed.

The frequency and severity of most ADRs were dosage related (figure 1). In those patients receiving gefitinib >525 mg/day, a higher incidence of CTC grade 3 or 4 ADRs and ADRs leading to withdrawal was seen in comparison with patients given ~500 mg/day (figure 1). The dosage-related nature of ADRs was highlighted by the observation that more dosage-limiting toxicities were generally observed in those patients who received ≥700 mg/day than those given <700 mg/day. Sixteen of 27 patients with dosage-limited toxicity were due to diarrhoea; of whom, 14 had received gefitinib ≥700 mg/day. Few patients required dosage reduction or interruption as a result of ADRs (7.0% and 6.7%, respectively) and for those patients who did, the majority had received ≥600 mg/day (73.7%). In contrast with dosage-related ADRs, the clinical benefit rate (partial response plus stable disease) was not dosage related. This is highlighted in figure 2,[22] where the incidence of skin rash in patients given gefitinib 50 and 1000 mg/day increased from approximately 35% to 85%, while the clinical benefit rate remained fairly constant at approximately 20%.

Less than one-sixth of patients (14.1%) experienced ophthalmological ADRs, with the most common being conjunctivitis (5.6%) and dry eyes (4.4%). Following the review of >830 slit-lamp examinations, an external Ophthalmology Advisory Board found no evidence of any consistent or significant ocular toxicity, with many of the observed eye events probably reflecting variance within a normal population or the frequent and intensive monitoring. The Board recommended that ophthalmological monitoring could be substantially reduced in future trials, as signals of potential ocular toxicity were infrequent and associated with easily recognisable symptoms, such that patients could seek medical advice if eye symptoms developed.

Expert cardiology review of data from >1600 ECGs obtained from patients in the phase I trials did not find any evidence that gefitinib prolonged PR or

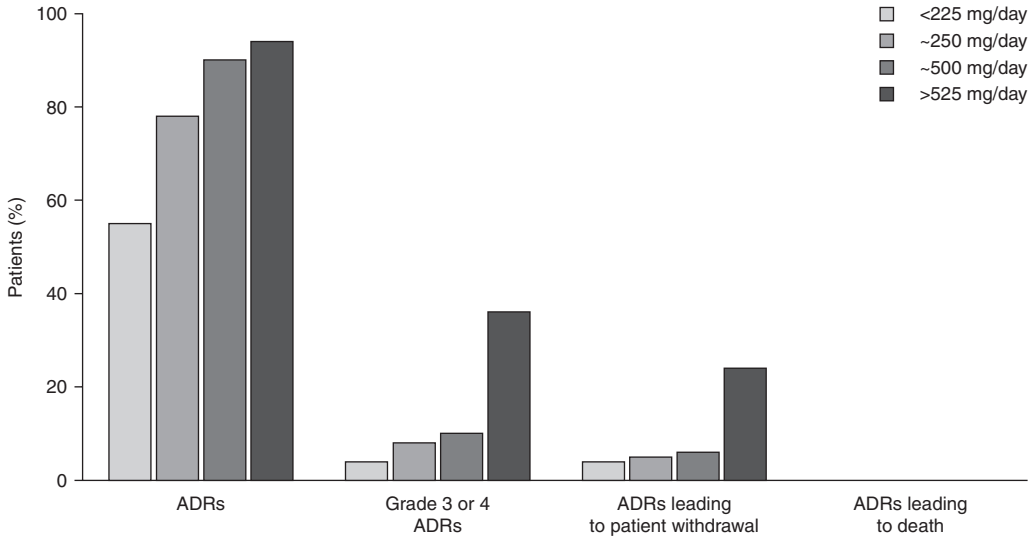

Fig. 1. Overview of adverse drug reactions (ADRs) in phase I multiple-dosage trials.

QT intervals over the dosage range studied (50–1000 mg/day). Consequently, there is no requirement for routine cardiac screening or monitoring of patients receiving gefitinib.

The phase I studies showed that dosages of ~250 mg/day were well tolerated, had consistent clinical benefit and maintained gefitinib exposure above the levels observed in patients taking 150 mg/day, which was the lowest dosage at which objective responses were seen, while dosages of ~500 mg/day were the highest dosages tolerated by most patients. Therefore, phase II studies employed gefitinib dosages of 250 and 500 mg/day.

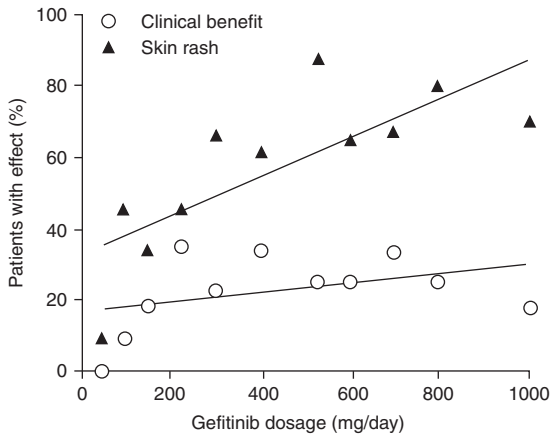

Fig. 2. Relationship between clinical benefit (objective response plus stable disease) and the occurrence of acneform skin rash in the four published phase I trials (50–1000 mg/day) [reproduced from Herbst,[22] © 2003, with permission from Elsevier].

3. Phase II Monotherapy Trials in Non-Small-Cell Lung Cancer

Two large, randomised, phase II clinical trials (IDEAL [IRESSA™ Dose Evaluation in Advanced Lung cancer] 1 and 2) recruited pretreated patients with locally advanced or metastatic NSCLC. IDEAL 1 recruited 209 patients across Europe, Australia, South Africa and Japan, all of whom had received one or two prior chemotherapy regimens, one of which had been platinum based.[23] IDEAL 2 recruited 216 patients in the US who had previously received two or more chemotherapy regimens, including a platinum compound and docetaxel given concurrently or as separate regimens.[24]

The safety profile in the IDEAL trials was comparable to that seen in the phase I trials, with no unexpected ADRs observed. An overview of ADRs in IDEAL 1 and 2 is shown in table IV. The most common ADRs in both IDEAL trials were CTC grade 1 or 2 skin rash and diarrhoea (table V), both of which usually occurred during the first month of

Table IV. Overview of adverse drug reactions (ADRs) in IDEAL (IRESSA™ Dose Evaluation in Advanced Lung cancer) 1 and 2 trials

ADRs [n (%)]	IDEAL 1		IDEAL 2	
	gefitinib 250 mg/day (n = 103)	gefitinib 500 mg/day (n = 106)	gefitinib 250 mg/day (n = 102)	gefitinib 500 mg/day (n = 114)
Total	88 (85.4)	102 (96.2)	74 (72.5)	97 (85.1)
Grade 3 or 4	9 (8.7)	32 (30.2)	7 (6.9)	20 (17.5)
Leading to withdrawal	2 (1.9)	10 (9.4)	1 (1.0)	5 (4.4)
Leading to death	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)

treatment and were manageable, non-cumulative and dosage related. Similar to the phase I trials, clinical benefit was not dosage related but the incidence of skin rash was (figure 3). Grade 3 or 4 ADRs were also dosage related, occurring in 52 patients receiving 500 mg/day (23.6%) compared with 16 patients receiving 250 mg/day (7.8%) [table IV]. The increased incidence in patients given 500 mg/day was accounted for primarily by diarrhoea (table V). The relationship between gefitinib dosage and the frequency and severity of ADRs was highlighted by the observation that grade 4 ADRs were seen in only two patients who received 250 mg/day (asthenia and thrombocytopenia), compared with nine patients who received 500 mg/day (with events of deep thrombophlebitis, anaemia, increased AST and ALT levels, pneumonia, skin rash, shock, dehydration and lung haemorrhage). Haematological toxicity and bone marrow depression were not typically observed. A low incidence of alopecia was observed in both IDEAL trials (1.0% for patients given 250 mg/day and 3.2% for patients given 500 mg/day) but

Table V. Patients experiencing an adverse drug reaction with an incidence of at least 10% in the IDEAL (IRESSA™ Dose Evaluation in Advanced Lung cancer) 1 and 2 trials

Adverse events by body system [n (%)][a]	IDEAL 1				IDEAL 2			
	gefitinib 250 mg/day (n = 103)		gefitinib 500 mg/day (n = 106)		gefitinib 250 mg/day (n = 102)		gefitinib 500 mg/day (n = 114)	
	all grades	grade 3 or 4	all grades	grade 3 or 4	all grades	grade 3 or 4	all grades	grade 3 or 4
Digestive								
Diarrhoea	39.8	0.0	57.6	6.6	48.0	1.0	66.7	5.3
Nausea	12.7	1.0	23.5	0.9	12.7	1.0	17.5	0.9
Vomiting	5.8	0.0	19.8	0.0	11.8	1.0	8.8	2.6
Anorexia	8.8	0.0	18.8	0.9	6.9	0.0	9.6	0.0
Metabolic and nutritional								
AST increased	10.6	0.0	22.7	2.8	1.0	0.0	2.6	1.8
ALT increased	12.6	1.9	23.5	5.6	1.0	0.0	2.6	1.8
Skin and appendages								
Rash	46.6	1.0	68.8	6.6	43.1	0.0	53.5	2.6
Acne	12.6	0.0	14.1	1.9	24.5	0.0	32.5	3.5
Dry skin	27.2	0.0	29.2	0.0	12.7	0.0	26.3	0.0
Pruritus	30.1	0.0	35.8	0.9	7.8	0.0	8.8	0.9
Whole body								
Asthenia	7.8	0.0	10.3	0.9	5.9	2.0	4.4	0.9
Other								
Epistaxis	1.9	0.0	11.3	0.0	2.0	1.0	2.6	0.0
Pain	9.7	0.0	16.1	0.0	2.0	0.0	0.9	0.0

a Patients may have had more than one adverse event.

ALT = alanine aminotransferase; **AST** = aspartate aminotransferase.

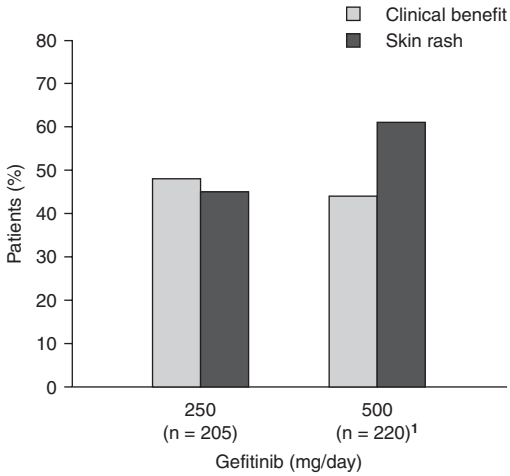

Fig. 3. The percentage of patients experiencing clinical benefit (objective response plus stable disease) and skin rash in the IDEAL (IRESSA™ Dose Evaluation in Advanced Lung cancer) 1 and 2 trials. **1** = 219 patients were included in the efficacy assessment.

it is difficult to evaluate the possibility of any causal relationship with gefitinib as patients had been heavily pretreated with chemotherapy.

Following the recommendations of the Ophthalmology Advisory Board from the phase I trials, ophthalmological monitoring was performed only at baseline and trial completion or withdrawal in both IDEAL trials. The most common ophthalmological ADRs were conjunctivitis (4.2%), blepharitis (3.1%) and dry eyes (2.6%); asymptomatic ophthalmological ADRs were not detected. These data confirmed that routine ophthalmological screening and monitoring are not required with gefitinib.

In IDEAL 1, interstitial lung disease (ILD)-type events were reported in two Japanese patients who received gefitinib 500 mg/day, while none were reported in IDEAL 2. One patient with interstitial pneumonia recovered following the withdrawal of gefitinib treatment due to disease progression (the withdrawal was not because of ILD). The other patient developed pneumonitis 3 days after stopping gefitinib because of severe fatigue, and a CT scan showed progression of carcinomatous pleuritis. Pneumonitis was ongoing 5 weeks later at the time of death, which was due to disease progression (not ILD).

Interruptions in therapy occurred less frequently in patients given 250 mg/day compared with 500 mg/day (31 vs 56 patients, respectively). Similarly, fewer patients taking 250 mg/day required dosage reduction compared with those taking 500 mg/day (1 vs 21 patients, respectively). Poorly tolerated or severe ADRs resulted in treatment withdrawal in only 18 patients (table IV); withdrawal of therapy in three patients given 250 mg/day was as a result of asthenia, bundle branch block and increased ALT levels, whereas the majority of ADRs necessitating withdrawal in 15 patients given 500 mg/day were gastrointestinal and skin disorders.

In both IDEAL trials, the manageable and non-cumulative nature of the majority of ADRs was emphasised by the fact that, following long-term follow-up, patients receiving gefitinib 250 and 500 mg/day continued receiving therapy for 93.8 and 84.8 days, respectively. Additionally, 70 patients continued to receive gefitinib for >6 months (35 patients taking 250 mg/day and 35 taking 500 mg/day).

No deaths in IDEAL 1 were regarded by the investigator as being gefitinib related (table IV). However, the death of one patient who received 500 mg/day in IDEAL 2, due to a lung haemorrhage in a centrally cavitating lesion, was considered by the reporting physician to be possibly both gefitinib and cancer related.

From these data, it is apparent that the two dosages of gefitinib (250 and 500 mg/day) were generally well tolerated in the majority of patients in the IDEAL trials, with 250 mg/day being better tolerated than 500 mg/day.

4. Additional Results from the Safety Database

The phase I and II safety data did not identify any special concerns regarding sex, ethnicity, age group, body mass index or performance status. No dosage adjustments or safety monitoring was considered necessary in any of these patient subgroups. These data were supported by an overall drug safety database that consists primarily of the global EAP and marketed use of gefitinib. By September 2004,

>53 000 patients had received gefitinib via the EAP, while approximately 120 000 patients had received gefitinib through normal market channels (table VI).[25] The safety data generated from the EAP and marketed use have enabled serious adverse events to be evaluated and any causal relationships identified. Continuing pharmacovigilance has confirmed that most serious ADRs are related to underlying disease, and that the safety profile of gefitinib is consistent with that observed in the phase I and II monotherapy trials.

As part of routine safety surveillance, a number of ILD-type events have been reported in patients receiving gefitinib. As of 1 September 2004, approximately 185 000 patients had received gefitinib worldwide, the incidence of reports of ILD-type events was 0.8%. The frequency of reports of ILD-type events in Japanese patients (1.6%) appears to be higher than in countries outside Japan (0.3%). These data are consistent with those presented 1 year ago.[26] The reason for this is unknown, although it may be related to population or environmental differences or differences in diagnostic criteria or clinical practice. Interestingly, this observed ethnic difference in reporting rates with gefitinib does not extend to other Asian territories, such as China, Hong Kong, Korea, Malaysia, the Philippines, Singapore, Taiwan and Thailand, where the frequency of reporting of ILD is comparable to that in other non-Japanese countries (0.3%). Further investigations to clarify the reasons for such an ethnic stratification in reports of ILD incidence following gefitinib treatment are underway.

Table VI. Characteristics of the overall safety database of gefitinib[a]

Data source	Number of patients
Primary safety database[b]	
IDEAL 1	209
IDEAL 2	216
Five phase I trials	270
Supportive safety data	
EAP	~53 556
Post-marketing use	~119 531
Other NSCLC studies	~7 258
Trials in other tumour types	~4 744
Total	**~185 784**

a Data as of 1 September 2004.

b Monotherapy.

EAP = Expanded Access Programme; **IDEAL** = IRESSA™ Dose Evaluation in Advanced Lung Cancer; **NSCLC** = non-small-cell lung cancer.

The safety database also identified that a small proportion of patients taking gefitinib concomitantly with warfarin had experienced an elevated international normalised ratio (INR) and/or bleeding event.[27]

As cytochrome P450 (CYP) 3A4 is involved in the hepatic metabolism of gefitinib,[28] it is possible that the safety profile of gefitinib could be affected in patients with impaired liver function due to liver metastases. The presence of liver metastases in the IDEAL trials (84 patients) did not appear to increase the likelihood of hepatic dysfunction or the frequency and severity of ADRs when compared with patients who did not have liver metastases. These observations were supported by data from a separate phase I trial in which the frequency and severity of ADRs were found to be comparable between patients with normal or moderate hepatic impairment due to liver metastases.[29]

Although only a small percentage of gefitinib is excreted unchanged via the kidneys (<4%),[28] the effect of impaired renal function on the safety profile of gefitinib was evaluated in the IDEAL trials. The safety profile of gefitinib in patients with mild to moderate renal impairment did not appear to be compromised in these trials, as the frequency of ADRs in 171 patients with mild to moderate renal function (creatinine clearance 30–80 mL/min) was similar to that seen for 230 patients with normal renal function (creatinine clearance >80 mL/min). As only one patient in the two studies had severe renal impairment, no conclusions can be drawn regarding the safety of gefitinib in patients with severe renal impairment.

Gefitinib can be given to patients who are also taking potent inhibitors of CYP3A4 activity (such as itraconazole), despite the resulting increase in plasma gefitinib concentrations.[30] Patients who receive itraconazole concomitantly with gefitinib are estimated to be 17% and 14% more likely to experience

diarrhoea or acne/skin rash, respectively, than patients who do not receive itraconazole.[31]

A high percentage of patients diagnosed with advanced NSCLC are elderly and/or unfit and often tolerate chemotherapy poorly ; therefore, data regarding the use of gefitinib in these subsets of patients are of great interest. A recent phase II study in 40 elderly pretreated patients with advanced NSCLC has shown that gefitinib is well tolerated in such patients, with generally mild adverse effects (mainly diarrhoea and skin toxicity).[32] Similarly, results from the EAP have shown that gefitinib is well tolerated in elderly patients and/or those who may not be suitable candidates for chemotherapy because of poor performance status or comorbid conditions.[33-35]

5. Recommendations for the Use of Gefitinib

Predictable, low-grade, mild to moderate, manageable diarrhoea and skin rash (mainly affecting the face and trunk with some limb involvement, manifesting as acneform eruptions or a maculopapular rash on an erythematous base) are the most commonly reported ADRs in patients receiving gefitinib.[27,36] Diarrhoea resolved spontaneously in the majority of patients and, where appropriate, antidiarrhoeals and rehydration were given.[23,24] Persistent diarrhoea may result in dehydration; if diarrhoea is seen it should be managed as clinically appropriate.[27] For those patients whose skin rash does not resolve spontaneously, several agents have been used with variable efficacy. Amongst a panel of IDEAL 2 investigators, some experts recommended topical clindamycin gel from the start of therapy, in addition to which some recommended a subsequent administration of a systemic antibiotic such as minocycline.[36] Other investigators recommended systemic antibiotics as initial therapy, in order to avoid topical application over a large body area. Some responses were also obtained with tretinoin. A good skin emollient was recommended for dry skin and the antihistamine hydroxyzine provided relief for patients with pruritus. Although the rashes associated with gefitinib are not caused by allergic reaction, some patients appeared to benefit from corticosteroids such as oral methylprednisolone, particularly for more intense flare-ups. Thus, although no specific treatment has been identified that is effective for all patients, gefitinib-associated skin reactions appear to be easily managed using a variety of treatments.

ILD has been observed infrequently in patients receiving gefitinib, with a lower incidence than that observed with other cancer therapies.[37] However, in the event of worsening respiratory symptoms (such as dyspnoea, cough or fever), gefitinib therapy should be interrupted and the symptoms investigated and managed. If ILD is confirmed, gefitinib treatment should be discontinued and the patient treated appropriately.

Although no safety issues were raised regarding the administration of gefitinib to patients with impaired liver function due to metastases, a small number of asymptomatic increases in liver transaminases (mainly CTC grade 1 or 2 elevations in AST or ALT levels) have been reported. Therefore, periodic liver function testing is appropriate for all patients who receive gefitinib.

INR elevations and/or minor bleeding events have been reported in a small proportion of patients taking warfarin. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR. It should be noted that this effect may not be due to a drug interaction but rather to the physiological condition of some of the patients receiving gefitinib.

6. Discussion

The favourable safety profile of gefitinib observed in five phase I trials in 270 patients with a range of solid tumours has been confirmed by safety data from two large phase II trials in 425 patients with locally advanced or metastatic NSCLC. Furthermore, substantial safety data from >185 000 patients have supported the findings from these clinical trials. Gefitinib is well tolerated, with the majority of ADRs being mild to moderate skin and gastrointestinal disorders. Safety is not compromised in patients with impaired hepatic or renal

function, the elderly, patients with poor performance status or weight loss due to disease or patients from different ethnic backgrounds. Indeed, gefitinib provides clinical benefit. In the phase I trials, objective responses were observed in ten patients (all of whom had NSCLC).[17-20] In the two large IDEAL trials, objective responses were seen in 11.8–18.4% of patients with advanced NSCLC given gefitinib 250 mg/day.[23,24] Therefore, gefitinib is not only well tolerated but is also clinically beneficial in patients with NSCLC. The clinical benefit of gefitinib has been highlighted in the IDEAL trials, where approximately 40% and 35% of symptomatic patients taking 250 or 500 mg/day, respectively, experienced symptom improvement.

In patients with locally advanced or metastatic disease, tolerability of treatment is of paramount importance. In the majority of patients, cytotoxic chemotherapy ADRs commonly include haematological toxicity (leading to infection and anaemia), neurotoxicity, nephrotoxicity, intolerable nausea and vomiting, and alopecia. Many of these ADRs often require hospitalisation of the patient and/or medical intervention. In contrast, gefitinib therapy does not appear to be associated with haematological toxicity, neurotoxicity or nephrotoxicity, and nausea and vomiting are generally mild to moderate. As of 1 September 2004, the incidence of reports of ILD-type events in patients who have received gefitinib worldwide is 0.8%, 1.6% in Japanese patients and 0.3% in countries outside Japan.[26] The findings from a recent retrospective survey of ILD-type events in 1976 patients treated with gefitinib in affiliated institutions of the West Japan Thoracic Oncology Group[38] confirm previous observations and evaluations in Japanese patients and are consistent with the warnings and precautions currently stated in the gefitinib core prescribing information. This is not the first time that ethnic stratification has been observed in the reporting of ILD-type events. A higher rate of ILD in Japan than in other countries has been seen with the disease-modifying antirheumatic drug leflunomide[39] and also in a recent review of national differences in adverse event terms used to describe the pulmonary adverse effects of drugs.[40] The frequency of lung cancer in patients with ILD-type events has also been found to be higher in Japan than in the US (48.2% vs 4.2%).[41] Standard lung cancer treatments, such as chemotherapy and radiotherapy, have been associated with incidences of ILD of at least 10%.[37,42-45] Overall, the favourable safety profile and clinical benefit of gefitinib observed in patients with locally advanced or metastatic disease suggest that gefitinib is different to current standard chemotherapy treatments.

7. Conclusions

This review of safety data from phase I and II trials shows that gefitinib monotherapy can result in low-grade, non-cumulative gastrointestinal disturbances and skin reactions. Mild to moderate increases in asymptomatic levels of liver transaminases and ILD in <1% of patients have also been observed. The recommended dosage of gefitinib (250 mg/day) determined from these phase I and II trials is one-third of the maximum tolerated dosage. As the phase I and II monotherapy trials have shown that increasing the dosage of gefitinib from 250 to 500 mg/day does not improve the objective response rate, it is clear that gefitinib 250 mg/day minimises ADRs without compromising efficacy. Such a favourable safety profile may have a significant impact not only on the patient but also on the economics of patient care, as the management of adverse effects is mainly in the outpatient setting and frequent safety monitoring is not required. In conclusion, the available data indicate that in patients with locally advanced or metastatic NSCLC for whom there is an unmet clinical need, gefitinib monotherapy is well tolerated.

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