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REVIEW

Ocular findings in patients with solid tumours treated with the epidermal growth factor receptor tyrosine kinase inhibitor gefitinib ('Iressa', ZD1839) in Phase I and II clinical trials

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Abstract

Purpose **To describe the strategy used for large-scale ophthalmological monitoring in the clinical development of the novel anticancer agent gefitinib ('Iressa', ZD1839), an epidermal growth factor receptor tyrosine kinase inhibitor, which had demonstrated ocular effects in preclinical animal models.**
Methods **In this extensive clinical trial programme, patients in Phase I and II trials underwent frequent and intensive ophthalmological monitoring at baseline and during the trials. Data were reviewed by an external independent Ophthalmology Advisory Board.**
Results **Ophthalmological data for 221 patients in Phase I trials of gefitinib and 425 patients in Phase II trials revealed no evidence of any consistent or drug-related ophthalmological toxicity. Interestingly, the baseline data revealed that, in an asymptomatic population, transient ophthalmological events are identified during monitoring.**
Conclusions **This study reports the methodology and normative data in an ophthalmological screening programme that should prove useful for future studies.**
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Keywords: cancer; EGFR; gefitinib; Iressa; ZD1839

Introduction

There are currently no data on the spectrum of ocular surface abnormalities in asymptomatic adults, as large-scale ophthalmological monitoring is not routinely carried out in most clinical trials. Here, we present baseline data from a large clinical trial programme of a novel anticancer agent in which patients underwent frequent biomicroscopic monitoring of the ocular surface.

Gefitinib ('Iressa', ZD1839) is an orally active epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that shows reversible cell growth inhibition *in vitro* and evidence of antitumour activity in clinical trials. In preclinical toxicity studies of gefitinib 40 mg/kg/day in rats and dogs, reversible thinning of corneal epithelium was observed in both species after 1 and 6 months.[1] Furthermore, in dogs treated with the highest dose of gefitinib for 6 months, the corneal opacification first observed at 1 month progressed on treatment and did not reverse during a 3-month withdrawal period.[1] Moreover, other EGFR inhibitors have caused similar corneal changes in preclinical models.[2,3]

These preclinical findings are consistent with the pharmacological actions of gefitinib. The EGFR is strongly expressed in the basal epithelial cells of limbal and conjunctival epithelia and throughout the corneal epithelium; however, little or no EGFR is seen in the superficial conjunctival or limbal epithelia,

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demonstrating that EGFR is preferentially expressed in basal epithelial cells that have the greatest proliferative potential.[4] The EGFR ligand, EGF, promotes migration and proliferation of epithelial cells, thus facilitating corneal epithelial wound healing.[5] Furthermore, endogenous EGF is synthesised by the lacrimal gland in response to corneal epithelial injury.[6] EGF is found in high concentrations in tears[7] and is important for normal ocular homeostasis.[8]

The preclinical results combined with the known ocular importance of the EGFR warranted ophthalmological monitoring during clinical trials of gefitinib. The initial dose-ranging Phase I trials of gefitinib were designed to determine its dose-limiting toxicity in patients with a range of advanced solid tumours. In these trials, patients underwent intensive and frequent ophthalmological monitoring. The monitoring procedures were reviewed and modified after the first trial (Trial 5). The data from all three Phase I trials were reviewed by an independent external Ophthalmology Advisory Board to determine the level of monitoring required in subsequent trials, including two large Phase II trials to investigate the antitumour activity of gefitinib monotherapy in advanced non-small-cell lung cancer (NSCLC). The advisory board constituted leading US and European ophthalmologists with expertise of both the cornea and drug-development issues. They were consulted prior to and during these Phase I studies and on an *ad hoc* basis for specific advice.

Here, we report the ocular findings in three Phase I, dose-escalation, multicentre trials of oral monotherapy gefitinib at doses up to 1000 mg/day in 221 patients with a range of solid malignancies (Trials 5, 11, and 12)[9–11] and 425 patients enrolled in two Phase II trials of gefitinib at two doses in patients with advanced NSCLC (IDEAL ['Iressa' Dose Evaluation in Advanced Lung cancer] 1 and 2).[12,13] Ocular data from these multicentre trials were standardised using pro forma ophthalmology records, with training given in assessment and documentation at study start-up (see Figure 1 for extensive ophthalmological parameters assessed). Clinically significant ophthalmological changes were reported as adverse events and discussed in depth with trial centre personnel when necessary, to obtain more information on the individual cases from a safety surveillance perspective and to ensure events were being described consistently.

Materials and methods

Phase I trials

Treatment

In the initial Phase I trial, gefitinib was administered once daily for 14 days followed by 14 days of observation in 28-day cycles (Trial 5). The subsequent Phase I trials were conducted using 28–day cycles of once-daily oral dosing (Trials 11 and 12). A range of different doses was used and for simplicity they have been grouped into four dose ranges, as follows: <225 mg/day (50, 100, and 150 mg/day); ~250 mg/day (225 and 300 mg/day); ~500 mg/day (400 and 525 mg/day); and >525 mg/day (600, 700, 800, and 1000 mg/day).

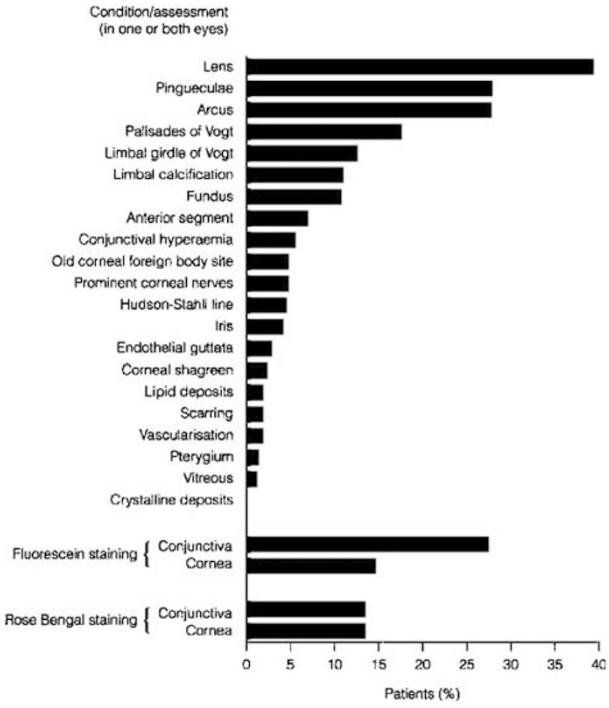

Figure 1 Baseline findings of slit-lamp examination in Phase I trials. *Anterior segment* includes iridoschisis, lower lid ptosis, blind shrunken eye since childhood, keratitic precipitates, lower lid notching, and loss of lashes; *Iris* includes dyscoria, prominent iris vessel, and synechiae; *Lens* includes cataract, opacity, and nuclear sclerosis; *Fundus* includes drusen, naevi, disc cupping, chorio-retinal atrophy, and diabetic retinopathy; *Vitreous* includes asteroid hyalosis.

Patients

Ophthalmological exclusion criteria were established in discussion with the independent Ophthalmology Advisory Board. These were: abnormality of cornea (other than scars, congenital abnormality or corneal tear-film insufficiency); currently receiving drugs with known corneal toxicity (eg hydroxychloroquine, amiodarone, tamoxifen, and chlorpromazine); history of dry-eye syndrome (eg Sjögren's syndrome); history of ocular surface abnormality (including Stevens–Johnson syndrome and alkali burns); eyes within a previous radiotherapy field; and current use of contact lenses (previous contact lens wearers were eligible if their eye examination was within normal limits).

Assessments
Ophthalmological assessments were established in discussion with the Ophthalmology Advisory Board. An ophthalmological examination was performed routinely at baseline, at Days 14 and 28 of each treatment period and on completion/withdrawal from the trial. This assessment included visual acuity, using a LogMAR illuminated distance vision or Snellen chart, and slit-lamp examination with fluorescein and Rose Bengal staining of the cornea and conjunctiva, including lid eversion to quantify tarsal conjunctival hyperaemia. Schirmer's test was used to measure the ability to produce tears over a 3-min period and patients were recorded as having 0–5, >5–10 or >10 mm of tears. Intraocular pressures were also recorded. In addition to routine monitoring, patients were assessed in the event of any ocular abnormalities or symptoms occurring between study visits.

Trial medication was to be stopped if a patient developed punctate staining with symptoms, conjunctival hyperaemia >1 quadrant or other objective findings considered more severe than this, for example, corneal epithelial defects or ulceration. Any clinically significant ophthalmological changes were recorded as adverse events using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 (Table 1).[14]

Phase II trials

In the absence of any consistent or significant ocular toxicity from the Phase I data, the Ophthalmology Advisory Board recommended that for the Phase II trials the inclusion/exclusion criteria could be relaxed and the level of monitoring could be substantially reduced, as any indicators of potential ocular toxicity were associated with easily recognised symptoms. Due to the observation of a few cases of aberrant lashes in Phase I trials, it was also recommended that investigators and patients should be made aware of potential corneal damage resulting from abnormal eyelash growth.

Treatment
In each of the Phase II trials, patients with previously treated but recurring NSCLC received oral gefitinib once daily at either 250 or 500 mg/day.

Patients
Patients were not excluded from these trials for any ocular conditions. However, those patients who had an ocular inflammation or infection had to have been fully treated before entry into the trial. Patients with an increased risk of corneal erosions (eg with a neuropathic keratopathy, diabetes, or anterior basement membrane dystrophy) were assessed frequently by an ophthalmologist during trial treatment.

Assessments
Following discussions with the Ophthalmology Advisory Board to establish what ophthalmological assessments were required, standard record forms were designed to capture this information. Prior to patient recruitment, training was given on correct assessment and documentation, including reporting of ocular adverse events (irrespective of causality).

An ophthalmological examination was performed routinely at baseline and on completion/withdrawal from the trial. This included assessment of visual acuity, quantification of conjunctival hyperaemia, slit-lamp examination with fluorescein staining, and a Schirmer's test (baseline only).

In the event of subjective symptoms of visual disturbance, eye pain or hyperaemia, trial medication was temporarily interrupted and a slit-lamp examination including eversion of the upper eyelid to check for the degree of hyperaemia, was conducted as soon as possible. Any clinically significant ophthalmological changes were recorded as adverse events using the NCI-CTC. An adverse event was defined, according to ICH E2A guidelines,[15] as the development of a new medical condition or the deterioration of a pre-existing medical condition following or during exposure to trial medication, whether or not considered causally related to the product.

Results

Phase I trials

Patients
A total of 221 patients with a wide range of solid tumours and prior anticancer treatments were enrolled in the three Phase I trials (Table 2). The median age (range) of the patients was 58 (27–90) years and half the population was male. The majority (65.6%) of patients had a World Health Organization performance status of *1* ('generally healthy but may not be able to do heavy physical work').

Baseline ophthalmological findings
More than 830 slit-lamp examinations were performed over the course of the three trials. Many patients entered into the trials had ophthalmological findings at baseline (Figure 1, $n = 173$ patients). Conjunctival hyperaemia was seen in 6% of patients at baseline, while the most common findings were pingueculae and arcus, both seen in 28% of patients. These findings were equally distributed across the dose groups (data not shown).

Table 1 Definition of ocular/visual adverse events by NCI-CTC grade[14]

	NCI-CTC grade				
	0	*1*	*2*	*3*	*4*
Cataract	None	Asymptomatic	Symptomatic, partial visual loss	Symptomatic, visual loss requiring treatment or interfering with function	—
Conjunctivitis	None	Abnormal ophthalmological changes, but asymptomatic or symptomatic without visual impairment (ie pain and irritation)	Symptomatic, and interfering with function, but not interfering with activities of daily living	Symptomatic, and interfering with activities of daily living	—
Dry eye	Normal	Mild, not requiring treatment	Moderate or requiring artificial tears	—	—
Glaucoma	None	Increase in intraocular pressure but no visual loss	Increase in intraocular pressure with retinal changes	Visual impairment	Unilateral or bilateral loss of vision (blindness)
Keratitis (corneal inflammation/ corneal ulceration)	None	Abnormal ophthalmological changes but asymptomatic or symptomatic without visual impairment (ie pain and irritation)	Symptomatic and interfering with function, but not interfering with activities of daily living	Symptomatic, and interfering with activities of daily living	Unilateral or bilateral loss of vision (blindness)
Tearing (watery eyes)	None	Mild: not interfering with function	Moderate: interfering with function, but not interfering with activities of daily living	Interfering with activities of daily living	—
Vision–blurred vision	Normal	—	Symptomatic, and interfering with function, but not interfering with activities of daily living	Symptomatic, and interfering with activities of daily living	—
Vision–double vision (diplopia)	Normal	—	Symptomatic, and interfering with function, but not interfering with activities of daily living	Symptomatic, and interfering with activities of daily living	—
Vision–flashing lights/floaters	Normal	Mild, not interfering with function	Symptomatic, and interfering with function, but not interfering with activities of daily living	Symptomatic, and interfering with activities of daily living	—
Vision–night blindness (nyctalopia)	Normal	Abnormal electro-retinography but asymptomatic	Symptomatic, and interfering with function, but not interfering with activities of daily living	Symptomatic, and interfering with activities of daily living	—
Vision–photophobia	Normal	—	Symptomatic, and interfering with function, but not interfering with activities of daily living	Symptomatic, and interfering with activities of daily living	—
Ocular/visual–other	Normal	Mild	Moderate	Severe	Unilateral or bilateral loss of vision (blindness)

Table 2 Patient demography in the Phase I trials

	Gefitinib dose level (mg/day)				
	<225 (n=42)	*~250 (n=69)*	*~500 (n=44)*	*>525 (n=66)*	*All (n=221)*
Age, median (range), years	53 (28–72)	56 (33–76)	59 (27–81)	60 (35–90)	58 (27–90)
Male/female, %	50/50	57/43	48/52	44/56	50/50
Performance status 0/1/2, %	21/71/7	29/70/0[a]	29/64/7	41/59/0	31/66/3
Primary tumour site, *n* (%)					
Breast	4 (9.5)	2 (2.9)	1 (2.3)	1 (1.5)	8 (3.6)
Colorectal	4 (9.5)	7 (10.1)	8 (18.2)	15 (22.7)	34 (15.4)
Gastric	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Head and neck	5 (11.9)	11 (15.9)	5 (11.4)	5 (7.6)	26 (11.8)
NSCLC	14 (33.3)	29 (42.0)	15 (34.1)	19 (28.8)	77 (34.8)
Oesophageal	0 (0.0)	2 (2.9)	2 (4.5)	0 (0.0)	4 (1.8)
Ovarian	4 (9.5)	7 (10.1)	7 (15.9)	15 (22.7)	33 (14.9)
Pancreatic	1 (2.4)	1 (1.4)	0 (0.0)	0 (0.0)	2 (0.9)
Prostate	1 (2.4)	7 (10.1)	2 (4.5)	9 (13.6)	19 (8.6)
Renal	3 (7.1)	1 (1.4)	0 (0.0)	0 (0.0)	4 (1.8)
Sarcoma	2 (4.8)	0 (0.0)	1 (2.3)	0 (0.0)	3 (1.4)
Other	3 (7.1)	2 (2.9)	3 (6.8)	2 (3.0)	10 (4.5)
Previous cancer treatment,[b] *n* (%)					
CIH	40 (95.2)	61 (88.4)	44 (100.0)	62 (93.9)	207 (93.7)
XRT	28 (66.7)	34 (49.3)	22 (50.0)	24 (36.4)	108 (48.9)
CIH + XRT	28 (66.7)	30 (43.5)	22 (50.0)	21 (31.8)	101 (45.7)
Surgery	11 (26.2)	34 (49.3)	21 (47.7)	45 (68.2)	111 (50.2)
Other	7 (16.7)	9 (13.0)	4 (9.1)	3 (4.5)	23 (10.4)
None	2 (4.8)	3 (4.3)	0 (0.0)	0 (0.0)	5 (2.3)

[a]Performance status not recorded for one patient in this group.
[b]Rows are not mutually exclusive.
CIH, chemotherapy, immunotherapy or hormonal therapy; XRT, radiotherapy.

The most common finding was lens abnormality, often defined as nuclear sclerosis, cataracts or opacities, which was seen in 39% of patients (Figure 1).

Changes in ophthalmological findings during gefitinib treatment

Approximately half (106) of the patients had a change from baseline in ophthalmological assessments performed during the trials (Figure 2). Most ophthalmological conditions that developed during the trials were transient, with only 34% of new ophthalmological events persisting for two or more consecutive assessments. Only 12% of patients developed conjunctival hyperaemia during the trials, with half of these events being transient.

Schirmer's tests revealed that over half the patients (54%) had no change in tear production at any time during the trials. Decreased tear production was seen in 41% of patients overall, with similar results being seen in each of the dose groups (Figure 3).

Ophthalmological events that were considered to be clinically significant were designated 'adverse events' (Table 3). The most common of these, seen in >5% of patients, were conjunctivitis (14.5%; 31 patients with NCI-CTC grade 1 or 2 and one patient with grade 3), dry eyes (8.1%; all NCI-CTC grade 1 or 2) and visual disturbance (7.2%; 15 patients with NCI-CTC grade 1 or 2 and one patient with grade 3 loss of visual acuity). In general, these adverse events did not appear to be related to either dose or treatment duration, and the majority resolved during the treatment period. However, dry eyes and corneal erosions showed some evidence of being dose related.

A small number of patients experienced adverse events of particular clinical interest with respect to preclinical findings and the pharmacological actions of gefitinib. One patient developed fine bilateral keratitic precipitates, which resolved following cessation of gefitinib. This patient had uveitis and a weakly positive ANA titre, which was treated with steroids. A second patient was described as having a 1×1 mm left corneal opacity. The underlying cause was not known; however, the opacity was not considered to be drug-related by the reporting physician and was ongoing at the time of

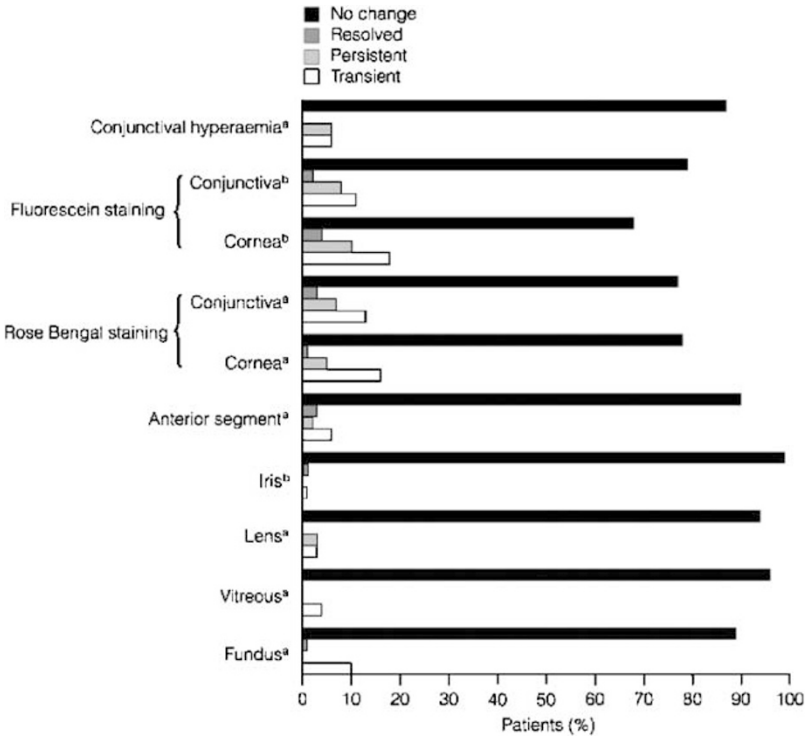

Figure 2 Changes from baseline in staining and additional ophthalmological checks during Phase I trials. *Anterior segment* persistent — keratitic precipitates, foreign body scar; transient — subepithelial opacity, conjunctional haemorrhage, aberrant eyelashes, blepharitis, jaundice; *Iris* transient — nodules; *Lens* persistent — nuclear sclerosis and cataract; transient — nuclear sclerosis; *Vitreous* transient — floaters; *Fundus* transient — Hollenhurst plaque, posterior vitreous detachment, minimal venous tortuosity, micro-aneurysm, supranasal peripapular myelin fibre. *No change*, patients did not show the condition at baseline or during the trial, or patients showed the condition at baseline and had the condition either persistently or transiently during the trial; *Resolved*, patients showed the condition at baseline but not during the trial; *Persistent*, patients did not have the condition at baseline but developed a persistent condition during the trial; *Transient*, patients did not have the condition at baseline but developed the condition transiently during the trial. [a]Trials 11 and 12 only, [b]Trial 5 data included.

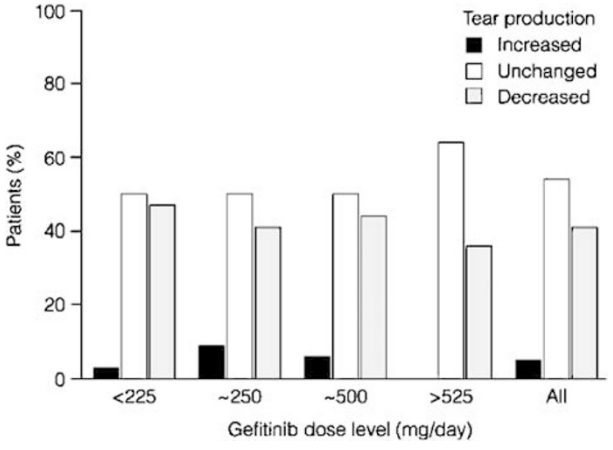

Figure 3 Worst change from baseline in Schirmer's test at any time during Phase I trials.

withdrawal due to disease progression. Five patients had corneal erosions that were considered by the investigator to be related to gefitinib treatment. One was a 70-year-old man receiving gefitinib 800 mg/day for prostate cancer. He had dry eyes at baseline (Schirmer's values: right 0–5 mm, left >5–10 mm). By Day 42 his condition had worsened to NCI-CTC grade 2, requiring artificial tears, and by Day 49 he developed grade 2 conjunctivitis. After two treatment periods, gefitinib therapy was interrupted and reduced to 600 mg/day due to an NCI-CTC grade 3 skin rash. During the third treatment period, he experienced eye discomfort and made an unscheduled visit to an ophthalmologist complaining of eye pain and redness. Slit-lamp examination revealed a serious NCI-CTC grade 3 corneal epithelial breakdown with a 3-mm central defect; the patient was withdrawn from the trial. Despite curative treatment, the defect increased to 6.5 mm. A review of photomicrographs of the defect site revealed an unreported ingrowing ectopic eyelash of the upper lid directly opposing the site of the corneal defect. The erosion was 95% healed 3 days after removal of the lash and subsequently healed completely. After 2 months, the patient developed an ingrowing lash on the lower lid. This was removed and was not associated with

Table 3 Ocular adverse events in Phase I trials, *n* (%)

Adverse events	*Gefitinib dose level (mg/day)*				
	<225 (n=42)	*~250 (n=69)*	*~500 (n=44)*	*>525 (n=66)*	*All (n=221)*
Total patients[a]	15 (35.7)	20 (29.0)	12 (27.3)	21 (31.8)	68 (30.8)
Conjunctivitis	9 (21.4)	10 (14.5)	4 (9.1)	9 (13.6)	32 (14.5)
Dry eyes	2 (4.8)	4 (5.8)	1 (2.3)	11 (16.7)	18 (8.1)
Visual disturbances[b]	6 (14.2)	9 (13.0)	1 (2.3)	0 (0.0)	16 (7.2)
Blepharitis	3 (7.1)	0 (0.0)	2 (4.5)	1 (1.5)	6 (2.7)
Superficial punctate keratopathy	0 (0.0)	2 (2.9)	0 (0.0)	2 (3.0)	4 (1.8)
Corneal erosion	0 (0.0)	0 (0.0)	2 (4.5)	2 (3.0)	4 (1.8)
Eye pain	2 (4.8)	0 (0.0)	2 (4.5)	0 (0.0)	4 (1.8)
Trichiasis	0 (0.0)	0 (0.0)	0 (0.0)	4 (6.1)	4 (1.8)
Eye disorder[c]	2 (4.8)	0 (0.0)	0 (0.0)	1 (1.5)	3 (1.4)
Subconjunctival haemorrhage	0 (0.0)	2 (2.9)	0 (0.0)	1 (1.5)	3 (1.4)
Corneal opacity	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.5)
Hyperlacrimation	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Cataract	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
Glaucoma	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (0.5)
Macular oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
Uveitis	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Unilateral scotomata	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (0.5)
Floaters	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.5)

[a]Patients may have had more than one adverse event.
[b]Includes blurred vision, abnormal vision, hemianopia (due to metastases) and photophobia.
[c]Pingueculae, iris nodules, corneal epithelial hyperplasia.

a corneal lesion. Two patients receiving gefitinib 600 and 800 mg/day also had corneal defects of NCI-CTC grades 2 and 3, respectively, which were associated with abnormal lashes. In both cases, the corneal defects healed rapidly after removal of the aberrant lashes. In one patient receiving gefitinib 400 mg/day, the NCI-CTC grade 1 erosion resolved after treatment cessation, while in one patient (gefitinib 525 mg/day), the grade 1 erosion resolved and the patient continued on treatment without recurrence. A further two patients reported ingrowing and abnormally long eyelashes, respectively (gefitinib 600 and 1000 mg/day), which were removed before any potential damage to the eye could occur. Corneal erosions and aberrant eyelashes were only observed at gefitinib doses of $\geqslant$400 mg/day.

Phase II trials

A total of 425 patients with pretreated advanced NSCLC were treated in the two Phase II trials (Table 4).

In these two studies, more than 500 slit-lamp examinations were performed. Eye symptoms/events were experienced by 102 (23.9%) patients (22.9% at 250 mg/day and 25.0% at 500 mg/day) during the trial period. The majority of these events were mild (grade 1, 77%) or moderate (grade 2, 22%). There were only two NCI-CTC grade 3 events reported, neither of which was considered by the investigator to be related to gefitinib treatment. The most common ocular adverse events seen in these trials were conjunctivitis (8.2%), dry eyes (4.0%), blepharitis (3.5%), and visual disturbance (3.1%), which included blurred vision, bilateral hemianopia, and photophobia (Table 5). There appeared to be a slight dose effect on conjunctivitis and events reported as corneal erosions and trichiasis. The remaining ocular adverse events, including those reported as superficial punctate keratopathy, did not show any evidence of being related to gefitinib dose.

Of the 35 reports of conjunctivitis (30 at NCI-CTC grade 1 and five at grade 2), 17 (48.6%) were thought by the investigator to be drug-related (2.4% at 250 mg/day and 5.9% at 500 mg/day). Conjunctivitis resolved in 28 of the 35 patients during the treatment period or after treatment was withdrawn. In the remaining seven patients, the event was ongoing at the time of withdrawal due to disease progression.

Superficial punctate keratopathy was observed in four patients at 250 mg/day and six patients at 500 mg/day. These events were all NCI-CTC grade 1, except for two grade 2 events at 500 mg/day. Five patients developed corneal erosions, four of whom were receiving the 500 mg/day dose. Two of these patients on 500 mg/day had NCI-CTC grade 1 erosions, one of which was not considered by the investigator to be related to gefitinib due to the patient's medical history. One patient with a history of corneal dystrophy and macular degeneration

Table 4 Patient demography in the Phase II trials

	Gefitinib dose level (mg/day)		
	250 (n = 205)	*500 (n = 220)*	*All (n = 425)*
Age, median (range), years	60 (28–85)	60 (30–80)	60 (28–85)
Male/female, %	67/33	60/40	64/36
Performance status 0/1/2, %	18/66/16	16/67/17	17/67/16
Previous cancer treatment, *n* (%)			
1 chemotherapy regimen	59 (28.8)	60 (27.3)	119 (28.0)
2 chemotherapy regimens	87 (42.2)	94 (42.7)	181 (42.5)
3 chemotherapy regimens	31 (15.0)	41 (18.6)	41 (18.6)
⩾4 chemotherapy regimens	28 (13.6)	25 (11.4)	125 (29.3)
Radiotherapy	125 (60.9)	122 (55.5)	247 (58.1)
Surgery	91 (44.2)	87 (39.5)	178 (41.8)
Other	3 (1.5)	9 (4.1)	12 (2.8)
Days on gefitinib, mean	79.6	73.7	76.6

Table 5 Ocular adverse events seen in Phase II trials, *n* (%)

Adverse event[a]	*Gefitinib dose level (mg/day)*		
	250 (n = 205)	*500 (n = 220)*	*All (n = 425)*
Conjunctivitis	15 (7.3)	20 (9.1)	35 (8.2)
Dry eyes	8 (3.9)	9 (4.1)	17 (4.0)
Blepharitis	8 (3.9)	7 (3.2)	15 (3.5)
Visual disturbance[b]	7 (3.4)	6 (2.7)	13 (3.1)
Superficial punctate keratopathy	4 (2.0)	6 (2.7)	10 (2.4)
Corneal erosion	1 (0.5)	4 (1.8)	5 (1.2)
Eye pain	5 (2.4)	3 (1.4)	8 (1.9)
Hyperlacrimation	3 (1.5)	5 (2.3)	8 (1.9)
Diplopia	2 (1.0)	2 (0.9)	4 (0.9)
Trichiasis	1 (0.5)	5 (2.3)	6 (1.4)
Cataract	1 (0.5)	1 (0.5)	2 (0.5)
Anisocoria	1 (0.5)	1 (0.5)	2 (0.5)
Bilateral macular oedema	1 (0.5)	0 (0.0)	1 (0.2)
Unilateral scotomata	0 (0.0)	1 (0.5)	1 (0.2)
Miosis	0 (0.0)	1 (0.5)	1 (0.2)
Ptosis	0 (0.0)	1 (0.5)	1 (0.2)
Subconjunctival haemorrhage	0 (0.0)	1 (0.5)	1 (0.2)

[a]Patients may have had more than one adverse event.
[b]Includes blurred vision, bilateral hemianopia and photophobia.

had a drug-related NCI-CTC grade 2 corneal erosion that resolved in 14 days following temporary withdrawal of gefitinib, while the fourth patient had a grade 3 corneal erosion that was considered to be traumatic and unrelated to trial treatment. The patient on 250 mg/day gefitinib had an NCI-CTC grade 2 corneal erosion that resolved 3 days after therapy ceased.

Events of dry eyes and blepharitis were mostly NCI-CTC grade 1 with a small number of grade 2 events. There was no difference in terms of frequency, causality, or severity between the 250 and 500 mg/day doses. In 65 and 93% of events of dry eyes and blepharitis, respectively, the investigator considered the event to be possibly related to trial treatment.

Six patients had mild-to-moderate trichiasis, one at 250 mg/day and five at 500 mg/day. One of these patients reported trichiasis as an adverse event on Days 43 and 120 of treatment. On Day 43 it was associated with NCI-CTC grade 2 blepharitis and ulceration of eyelid skin, and on Day 120 with grade 2 blepharitis.

Discussion

The baseline data in these trials revealed that, in an asymptomatic population, events on the ocular surface are identified during frequent and intensive monitoring. However, the majority of these were found to be transient.

Gefitinib is the first in a new class of biologically targeted anticancer agents that inhibit the EGFR. It has shown unprecedented antitumour activity in heavily pretreated patients with advanced NSCLC and is generally well tolerated, with the most common adverse events being mild diarrhoea and skin rash. It is not typically associated with the haematological side effects seen with conventional chemotherapy.[12,13] Gefitinib has now been licensed for use in NSCLC in 24 countries, including the USA, Australia, Canada, Switzerland, and Japan, and, as of March 2004, has been used in more than 132,000 patients. For many oncologists, novel targeted therapies such as gefitinib represent the future of anticancer treatment; therefore, it is important that all associated safety issues, including potential ophthalmological toxicity, are fully understood.

Gefitinib appears to be unrelated to any significant ocular events at the doses used in these studies. There appears to be an increased likelihood of dry eyes at doses ⩾525 mg/day. In the Phase I trials there was no evidence of any consistent or drug-related ophthalmological toxicity and many of the events observed were thought to reflect the variance within a normal population. The most clinically significant ophthalmological events reported in these trials were infrequent reversible corneal erosions, which all occurred at doses higher than the currently recommended dose of gefitinib (250 mg/day). Furthermore, several of these events were associated with abnormal eyelash growth and were heralded by symptoms of pain or discomfort. The corneal erosions healed rapidly on removal of the abnormal lashes. Patients could readily monitor this condition and lashes can be removed before any corneal damage occurs.

Interestingly, these trials did not reveal any asymptomatic findings representative of those detected in preclinical animal studies (rough appearance of cornea, diffuse corneal translucency, and corneal atrophy).

These results are supported by data from the two large Phase II trials. Gefitinib at 250 mg/day has been received by more than 46,000 patients as part of the Expanded Access Programme that allows gefitinib to be given on a compassionate basis to cancer patients with no other treatment options. A small number of ocular events has been reported, which were similar to those seen in the gefitinib trial programme, but there has been no evidence of significant ocular toxicity in the Expanded Access Programme, thus supporting the data from the clinical trials.

Mild conjunctival hyperaemia, mild, and reversible superficial punctate keratopathy, blepharitis, and trichiasis were found in a small percentage of patients in the clinical trial programme. In general, these findings are nonspecific and could be caused by any of several factors besides gefitinib, including age or pre-existing keratoconjunctivitis sicca. One possible explanation for these minimal ocular findings is pre-existing dry-eye syndrome due to damage to the tear-film producing ocular structures caused by previous chemotherapy. Any such damage could have been exacerbated by the use of an EGFR-TKI. EGFR expression has been demonstrated in the ocular surface epithelia in humans, particularly in the basal epithelial cells, which have the greatest proliferative potential.[4] Furthermore, it has been shown that the expression of EGFR in the conjunctival epithelium is significantly greater in eyes with keratoconjunctivitis sicca than in normal eyes.[16] The increased expression of these receptors has been positively correlated with ocular surface dye staining. It has been suggested that the balance of cytokines in the tear fluid and conjunctival epithelium is altered in Sjögren's syndrome and that the severity of keratoconjunctivitis sicca increases as tear fluid EGF concentration decreases.[17] Thus, it is possible that in patients who have pre-existing keratoconjunctivitis sicca, addition of an EGFR-TKI may exacerbate the signs and symptoms of this condition. The prophylactic use of topical lubricating drops (artificial tears) would be an appropriate way to prevent mild keratoconjunctivitis sicca in patients predisposed to this condition.

Meibomitis (inflammation of the sebaceous meibomian glands at the base of the lashes) was seen in a few patients in the clinical trial programme and was generally mild and reversible. An acneiform rash on the face and body is a well-known side effect of most EGFR-TKIs.[9] It is possible that meibomian gland inflammation and overactivity, like the acneiform rash, can occur secondary to gefitinib. Meibomitis may be a contributing factor to other ocular findings observed in the current study, such as trichiasis, mild superficial keratopathy, conjunctival hyperaemia, and dry-eye syndrome.

In conclusion, results from the comprehensive ophthalmological monitoring performed in these Phase I and II trials, including more than 1300 slit-lamp examinations, did not reveal any serious adverse ocular events representative of those seen in preclinical studies. Moreover, with the exception of minor and treatable superficial punctate keratopathy, dry eyes, blepharitis, conjunctivitis, and trichiasis in a few patients, no consistent drug-related ocular toxicity was seen in these trials. Gefitinib was associated with far less ocular toxicity than conventional chemotherapy.[18] There is therefore no evidence to suggest a need for routine ophthalmological surveillance of patients receiving gefitinib. As is the case with any chemotherapeutic agent, patients ought to be made aware that they should seek advice if they develop any new ocular symptoms while receiving this novel drug.

As large-scale ophthalmological monitoring is not routinely carried out in clinical trials, there are no standard procedures for undertaking such screening. The methodology for assessing the ocular effects of gefitinib used in these studies may assist others in planning their approach when studying other novel therapeutic agents that may be expected to have ocular effects. Furthermore, the results seen with gefitinib, the first in a new class of small molecule EGFR-TKIs, may go some way towards predicting the effects of other similar agents currently under development.

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