Basic Clinical Parameters Predict Gefitinib Efficacy in Non-small Cell Lung Cancer

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Abstract. *Background: In epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC), the tyrosine-kinase inhibitor gefitinib is in broad use. We retrospectively analysed data for 82 patients with advanced NSCLC treated with gefitinib and correlated benefits with clinical baseline and therapy-related parameters. Patients: Of all patients 48/82 were male; the median age at start of gefitinib was 67.2 years; 14/58 informative patients were never-smokers; 57/82 patients suffered from adenocarcinoma, including 7 with bronchoalveolar-carcinomas. Results: As to be expected, partial remission was observed in 10% of patients, stable disease in 29%, progression-free survival was 3.1 months and overall survival 9.2 months. Gefitinib was more efficacious in women, never-smokers and patients with bronchoalveolar-carcinoma. Furthermore, anemia and elevated C-reactive protein levels were unfavourable for therapeutic efficacy. Patients developing skin reactions under gefitinib achieved response far more frequently, with longer progression-free survival and overall survival. Conclusion: Basic clinical parameters are good predictors for response to EGFR tyrosine-kinase inhibitor therapy, which may be of value if EGFR mutation status is not available.*

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Lung cancer is a leading cause of cancer-related death worldwide. The majority of patients are diagnosed in an advanced stage of disease with limited therapeutic options. Chemotherapy and standard platinum-based regimens have reached a therapeutic plateau and new targeted agents have been introduced in the clinical practice (1, 2). One of the most studied molecular targets is the epidermal growth factor receptor (EGFR) signalling pathway, which can be inhibited by selective tyrosine kinase inhibitors (TKI) or monoclonal antibodies towards the extracellular domain of the receptor (3). Gefitinib is an oral EGFR TKI and was recently approved for the treatment of EGFR-mutated non-small cell lung cancer (NSCLC). Prior to this, gefitinib was given to pre-treated patients in an expanded access programme (EAP) between 2001 and 2006.

The combination of gefitinib with platinum-based chemotherapy *versus* chemotherapy alone in unselected patients with advanced NSCLC only did not bring about increased efficacy of the combination in terms of response, progression-free survival (PFS) or overall survival (OS) (4, 5). In second-line therapy of NSCLC, gefitinib was not inferior to docetaxel and had a tolerable side-effect profile (6). However, gefitinib did not improve OS in the entire cohort when compared to best supportive care in a large phase III trial (ISEL) (7).

On the other hand, subgroup analyses of several studies have shown that women, patients with an adenocarcinoma, never-smokers, and patients of Asian origin manifested improved response rates and benefits from EGFR-TKI therapy (8, 9). Therefore, different studies performed a preselection for responsiveness to EGFR-TKI (never-smokers or former light smokers, adenocarcinoma histology, Asian ethnicity) and gefitinib showed a significant prolonged PFS compared to chemotherapy (10). The IPASS study included a large biomarker program and identified the *EGFR*

mutation status as best predictor for response to therapy (11). Thus, gefitinib was approved for the treatment of patients harbouring recurrent activating mutations in the tyrosine kinase domain (exons 18, 19, and 21).

We retrospectively analysed data for 82 patients with advanced NSCLC treated with gefitinib within Astra Zeneca's International EAP in three centres in Austria. The aim of this evaluation was to investigate the efficacy and toxicity of gefitinib in the routine clinical setting and define clinical features predictive of therapeutic efficacy.

Patients and Methods

Patients. The records of 82 patients treated with gefitinib between 2001 and 2006 at the Medical University of Innsbruck, the Natters Hospital, Tyrol and the Hospital of Hietzing, Vienna were retrospectively analysed. The patients were treated within the manufacturer's "Iressa Named Patient EAP", and each patient's informed consent was obtained. The majority of patients were documented in detail within the ongoing project "Twelve Year Retrospective Analysis of Lung Cancer (TYROL study)", which aims at describing the daily routine setting of lung cancer in terms of symptomatology, comorbidity, laboratory findings, therapeutic sequence and outcome (12). The analysis of the TYROL study's data set was approved by the Ethics Board of Innsbruck.

In accordance with the manufacturer's recommendation at the time of conduction of the EAP in NSCLC, gefitinib was used as monotherapy at a daily dose of 250 mg in pretreated NSCLC. In this EAP, it was pre-specified that patients were required to have histologically or cytologically confirmed NSCLC, had received at least one course of standard systemic chemotherapy or radiation therapy, or were ineligible for chemotherapy or radiotherapy, were 18 years or older and had given written informed consent. The period of gefitinib administration, adverse events, reasons for modification or stopping of treatment, and survival updates were reported to EAP headquarters.

Response evaluation. Patients who received at least one dose of gefitinib were assessed for efficacy and safety. Response evaluation was routinely performed following every two to three cycles (months) and after termination of therapy, *i.e.* usually at documentation of progressive disease (PD) or intolerable toxicity. Thus, response was documented as 'best response' at any point in time during gefitinib therapy, and had to last for at least four weeks. Response was evaluated according to RECIST criteria for target and non-target lesions (13), but no central radiogram review was conducted. PFS was defined as the time from the first dose of gefitinib to disease progression or death, whichever occurred first. OS was measured from the initiation of gefitinib therapy until death of any cause.

Statistical considerations. Comparison of response rates between patient subgroups at baseline was carried out using Pearson's chi-square test. Cut-off values for presence of anaemia and inflammatory reactions were defined as haemoglobin <12 g/dl and C-reactive protein (CRP) >1 mg/dl, respectively. These cut-off values were predefined in the TYROL registry. Event-related data (PFS and OS) were estimated using the Kaplan-Meier method, and comparison of outcomes between categorical subgroups was made using the log-rank test. Univariate analysis was used to determine which baseline characteristics were associated with PFS and OS. For those found to be associated with PFS and OS ($p \leq 0.10$), hazard ratios were calculated using the multivariate Cox regression analysis. The significance level was set at $p<0.05$, in two-sided tests.

Table I. *Patient demographics and baseline characteristics at the start of gefitinib therapy (n=82).*

Characteristic	N	%
Male	48	59
Median age (range), years	67.2 (41.3-83.4)	
Prior chemotherapy lines, including (neo)adjuvant therapy	2 (0-5)	
Histology		
Adenocarcinoma	50	61
Epidermoid carcinoma	16	20
Bronchoalveolar carcinoma	7	9
Large cell carcinoma	4	5
Adenosquamous carcinoma	2	2
Undifferentiated carcinoma	2	2
Large cell neuroendocrine carcinoma	1	1
Performance status (WHO grade)		
0-1	19	23
2	33	40
3	16	20
4	6	7
Unknown	8	10
Abnormal laboratory values*		
Anaemia	15/51	29
Leucocytosis	3/51	6
Lactate dehydrogenase elevation	15/46	33
C-Reactive protein elevated	32/47	68
Median number of gefitinib cycles, in months (range)	3 (1-78)	

*Data for laboratory analysis was not always available for all 82 patients.

Results

Patient characteristics. This survey included 82 patients who had received gefitinib as monotherapy in three Austrian centres between December 3, 2001 and May 2, 2006. Patient demographics and baseline characteristics are detailed in Table I. Forty-eight patients (59%) were male, and the median age at the start of gefitinib was 67.2 years (range, 41.3-83.4 years). All patients were suffering from stage IV NSCLC, and had received a median of two prior chemotherapy lines including neo-adjuvant therapies (range, 0 to 5 lines). Twenty patients (24%) had been subjected to radical surgery with curative intent but experienced disease relapse. The majority of patients had adenocarcinoma (n=57) including bronchoalveolar carcinoma (BAC, n=7). At study entry, most patients had a favourable performance status and had normal haemoglobin levels. Of note, a significant proportion of patients exhibited laboratory signs of inflammatory reaction (C-reactive protein, CRP) and more aggressive tumour behaviour as defined by

Table II. *Univariate analysis for association of baseline characteristics with therapeutic response, progression free survival (PFS) and overall survival (OS).*

Characteristic	No. of patients	ORR, n (%)	*p*-value	CBR	*p*-value	Median PFS, months	p-value	Median OS, months	*p*-value
All	82	8 (10)		32 (39)		3.1		9.2	
Gender									
Male	48	2 (4)	0.061*	12 (25)	0.002	2.5	0.001	5.9	0.059
Female	34	6 (18)		20 (59)		7.3		13.8	
ECOG PS									
0-1	19	3 (16)	0.415	11 (58)	0.074	7.3	0.236	14.0	0.249
≥2	55	5 (9)		19 (34)		2.8		7.5	
Age, years									
<67.2	41	2 (5)	0.264*	15 (37)	0.651	2.5	0.239	12.0	0.863
≥67.2	41	6 (15)		17 (42)		3.9		8.5	
Smoking									
Never	14	2 (14)	0.322	10 (71)	0.011	9.2	0.002	8.0	0.001
Ever	47	3 (6)		14 (30)		2.9		22.2	
Histology									
BAC	7	0 (0)	1.000*	5 (71)	0.104*	40.9	0.030	44.0	0.004
Rest	75	8 (11)		27 (36)		2.9		7.8	
Histology									
Adenocarcinoma**	57	7 (12)	0.424*	24 (42)	0.388	3.6	0.772	8.5	0.617
Other	25	1 (4)		8 (32)		2.8		12.1	
Hemoglobine									
≥12 g/dl	36	5 (14)	0.657*	16 (44)	0.348*	2.9	0.009	12.1	0.001
<12 g/dl	15	1 (7)		4 (27)		2.5		3.1	
CRP									
<1 mg/dl	15	4 (27)	0.072	12 (80)	<0.001	8.2	0.001	14.9	0.023
≥1 mg/dl	32	2 (6)		7 (22)		2.5		5.1	
LDH									
Normal	31	4 (13)	1.000*	15 (48)	0.210*	2.9	0.499	9.5	0.635
Elevated	15	1 (7)		4 (27)		2.0		3.1	
Therapy line									
First/2nd	33	2 (6)	0.358	10 (30)	0.250	3.6	0.933	13.7	0.261
3rd	32	5 (16)		16 (50)		2.9		7.8	
4th or higher	17	1 (6)		6 (35)		2.8		6.6	
No. of cycles									
1-3	46	0 (0)	0.001	3 (7)	<0.001	2.0	<0.001	3.5	<0.001
>3	36	8 (22)		29 (81)		9.1		14.1	
Skin toxicity									
None	39	2 (25)	0.137	9 (28)	<0.001	2.5	<0.001	6.8	<0.001
Rash***	35	6 (75)		23 (72)		9.3		14.9	
Response									
PR	8						9.8	<0.001	19.6
<0.001									
SD	24						9.5		18.0
Other	50						2.1		3.5

BAC, Bronchoalveolar carcinoma; PR: partial response; SD: stable disease; CBR: clinical benefit rate (PR and SD); CRP, C-reactive protein; LDH, lactate dehydrogenase; ORR, overall response rate. *Fisher´s exact test; **including BAC; ***including acne-like skin alterations and palmar-plantar erythrodysaestesia.

elevated lactate dehydrogenase (LDH) (Table I). The median number of cycles (months) within gefitinib therapy was 3 (range, 1 to 78 cycles).

Response. Response to gefitinib was evaluated in 67 patients. In the remaining 15 patients, response could not be assessed due to premature death during therapy (n=8, fatal lung haemorrhage in one and pneumonia in another; unknown in six) or interruption of therapy with loss of follow-up (n=7). An objective response during the course of gefitinib administration ('best response') was documented in 8/82 patients (overall response rate (ORR) 10%, all partial response (PR)). Stable disease (SD) at one or several consecutive radiological evaluations (usually every 2-4

months) was observed in 24/82 patients (29%), whereas 35/82 patients (43%) showed PD at the first planned restaging after the start of gefitinib therapy. In summary, the clinical benefit rate (CBR=PR+SD) with gefitinib was 39% (32/82 patients). ORR and CBR according to patients' characteristics and prior therapies are detailed in Table II. Objective response was closely related to the duration of gefitinib administration (>3 months). Higher CBR was closely related to the following clinical features: female sex, never-smoking status, normal CRP level, duration of gefitinib administration >3 months, and occurrence of skin reaction, including rash, exanthema or palmar-plantar erythrodysaesthesia (PPE) (Table II).

Progression-free survival. At the time of the last update, 65 patients had documented PD, and 11 patients had died without documented PD (in whom the reasons for death were known in two cases, see above). The remaining six patients were alive without PD at the last contact and the data were graded at that point. The median PFS for all 82 patients after start of gefitinib therapy was 3.1 months, well in line with published data (14-16). A shorter PFS was closely related to serum markers pointing to tumour activity and inflammatory reaction (*i.e.* CRP elevation, decreased haemoglobin, Figure 1). Interestingly, there was no difference in PFS, regardless of whether gefitinib was administered as first-line or higher therapy (Figure 2). The median PFS according to different clinical characteristics are detailed in Table II. In univariate analysis, longer PFS was significantly associated with female gender, never-smoker status, histology of BAC, absence of anaemia, absence of CRP elevation, administration of gefitinib >3 months, manifestation of skin reaction, and achievement of response or SD. It was previously reported that disease stabilization on treatment with gefitinib was a positive predictor of survival (8). In line with those data, our results show that patients with SD *versus* those with PR on gefitinib did not differ with respect to PFS (Figure 3). Multivariate Cox regression analysis was performed, and both pretreatment baseline characteristics (namely gender and BAC histology) and treatment-related parameters (achievement of response or SD, length of gefitinib therapy and skin reaction) which were significant in the univariate analysis were included (n=74). The parameters of smoking status, CRP and haemoglobin could not be included in multivariate analysis because only limited data were available (Table II). According to multivariate analysis in this model, the independent risk factors for longer PFS were response or SD (hazard ratio=0.068; 95% confidence interval [95% CI]=0.023–0.204; $p<0.001$); skin reaction (hazard ratio=0.419; 95% CI=0.214-0.820; $p=0.011$); and female gender (hazard ratio=0.536; 95% CI=0.301-0.952; $p=0.033$).

Overall survival. At the last follow-up, 71 patients had died. The median OS after initiation of gefitinib was 9.2 months.

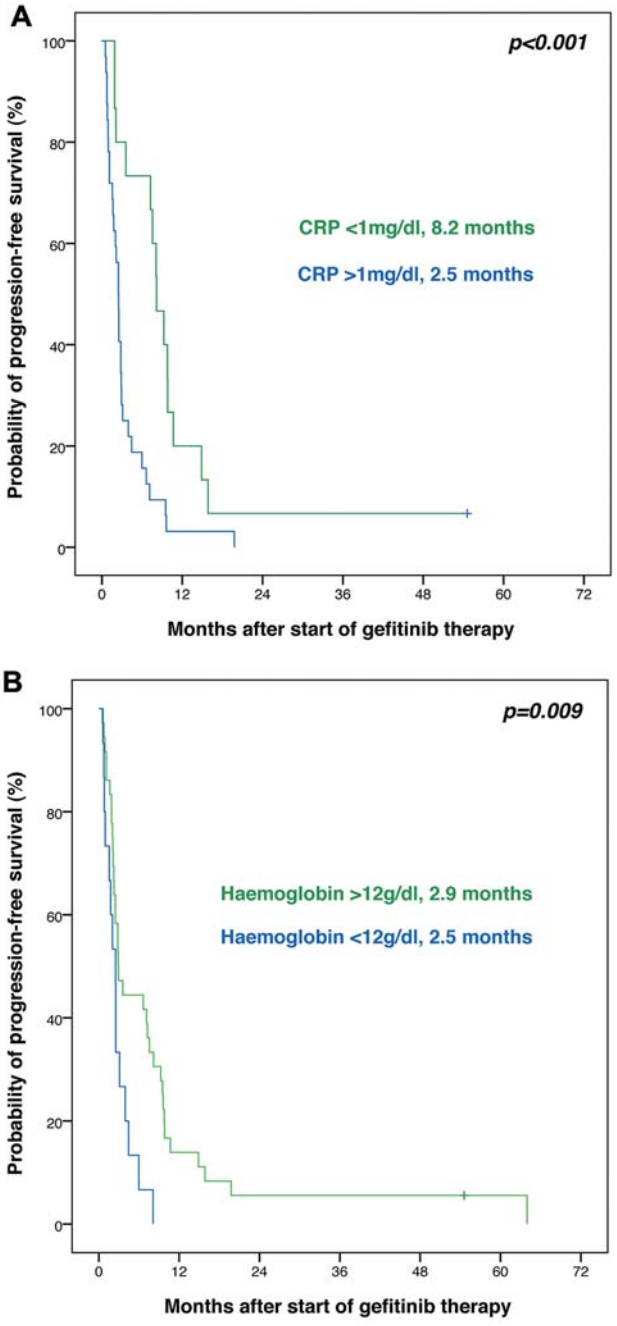

Figure 1. *Kaplan-Meier plot illustrating progression-free survival (PFS) in patients with non-small cell lung cancer (NSCLC) who received gefitinib according to baseline laboratory examinations of CRP (A) and haemoglobin (B).*

OS was significantly longer in patients who never smoked, patients with BAC histology, normal haemoglobin, normal CRP, skin reaction, >3 months of gefitinib therapy, and achievement of PR or SD (Table II). In analogy with PFS, patients experiencing SD had similar OS to those with PR (Table II).

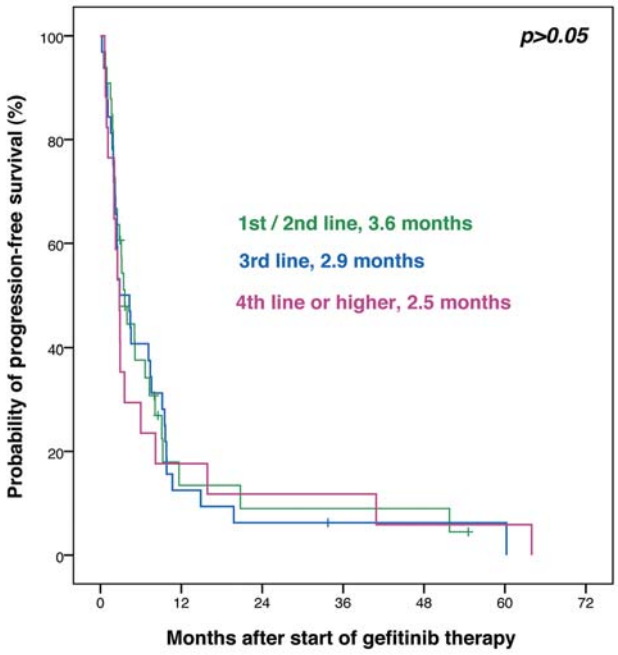

Figure 2. *Kaplan-Meier plot illustrating progression-free survival (PFS) in patients with non-small cell lung cancer (NSCLC), who received gefitinib. The line of therapy in which gefitinib was applied did not influence therapy outcome. Even in higher treatment lines gefitinib was effective.*

In multivariate Cox regression analysis (including the characteristics BAC histology, achievement of PR or SD, length of gefitinib therapy and skin reaction), independent risk factors for longer OS were clinical benefit (hazard ratio=0.363; 95%CI=0.164-0.803; p=0.012) and BAC histology (hazard ratio=0.346; 95% CI=0.135-0.884; p=0.027).

Therapies after gefitinib. Following disease progression after gefitinib, 19 patients received another line of palliative systemic therapy, and one patient had palliative resection of the main tumour mass. Following gefitinib, the most common subsequent therapies were: gemcitabine (n=8); vinorelbine (n=3); pemetrexed (n=2), cisplatinum/vinorelbine, temozolamide, liposomal doxorubicin, cisplatinum/etoposide, and mitomycin/iphosphamide/carboplatin (n=1 each).

Safety. Data on side-effects with gefitinib therapy were not available for 8 patients in this survey. For the remaining 74 patients, the most common side-effects reported, of any grade, were exanthema (n=22, 30%), acne (n=17, 23%), diarrhaea (n=14, 19%), fatigue (n=7, 10%), fever and infection (n=6, 8%, of which one was fatal), and PPE (n=5 [7%]). Other reported side-effects were: cramps in the calf, n=3), nausea/emesis (n=3), obstipation (n=2), hyponatremia

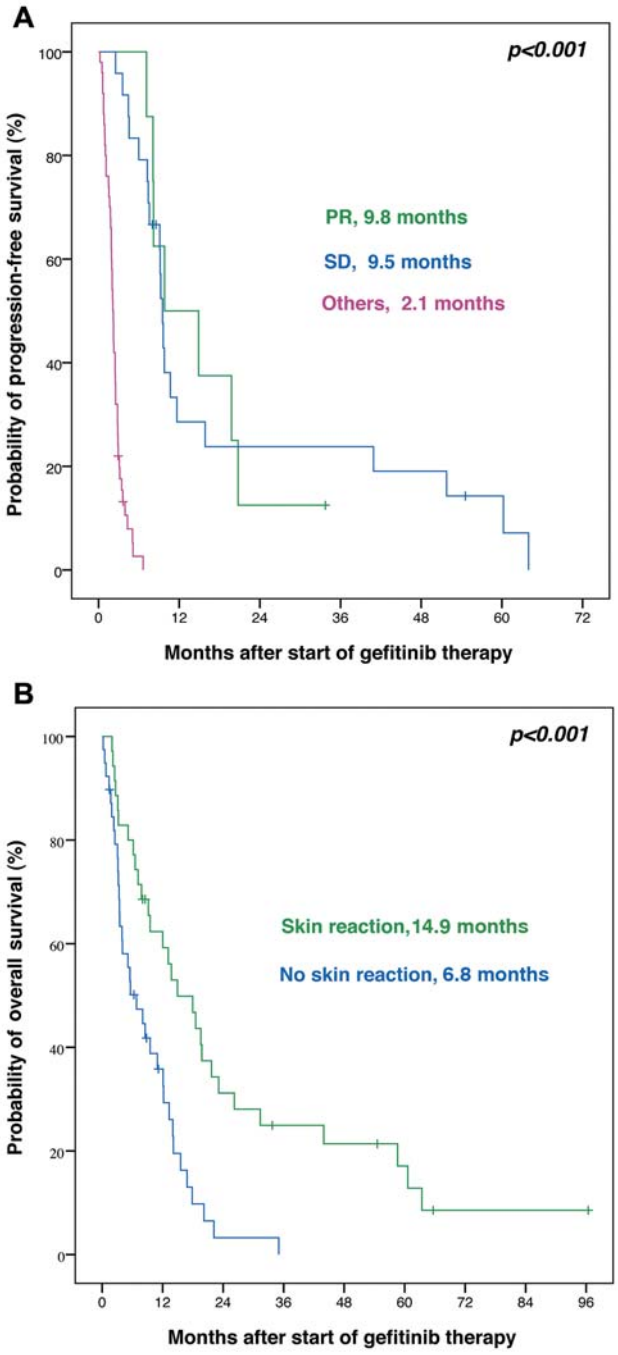

Figure 3. *Kaplan-Meier plot illustrating survival in patients with non-small cell lung cancer (NSCLC) who received gefitinib. Therapy-related factors influencing outcome are shown. A: Patients even with disease stabilization had a progression free survival equal to patients who showed an objective response to therapy. B: The appearance of a skin reaction correlated with a prolonged overall survival with gefitinib therapy.*

(n=2), interstitial pneumonitis, hypertension, conjunctivitis, toxic hepatopathy, increasing polyneuropathy, and fatal lung haemorrhage (n=1 each).

Discussion

The identification of predictive markers for customized anti tumor therapy is a major goal in modern lung cancer treatment. Nowadays, it is well established that *EGFR* mutational status is the best predictor of gefitinib efficacy, and a positive result for *EGFR* mutation is a prerequisite for administration of gefitinib within licensed approval (reviewed in (17)). A decade ago, gefitinib was assessed in unselected patients, as well as in subpopulations which were more likely to respond to therapy based on ethnic and clinical characteristics (8). An EAP enabled physicians to apply gefitinib in NSCLC based on encouraging study data, and, at that time, *EGFR* mutational status was not a prerequisite for gefitinib use (18, 19). We retrospectively analysed the data of patients who had been treated with gefitinib in three different hospitals in Austria within the EAP between 2001 and 2006. Overall, gefitinib resulted in a clinical benefit rate (PR+SD) in 39% of treated patients leading to a PFS of 3.1 months and an OS of 9.2 months. These data are in line with already published data (14-16).

In order to define diverse simple clinical parameters predicitive of a favourable outcome by gefitinib in NSCLC, clinical and laboratory parameters at initiation of gefitinib were documented and viewed in relation to therapeutic efficacy. The analyses of subgroups verified that women, never-smokers and patients with tumors with BAC histology responded with greater likelihood to gefitinib, in line with published data (14). Anaemia and increased CRP levels correlated unfavourably with therapeutic efficacy, an observation which has not been described thus far in context with gefitinib (Figure 1). Even more interestingly, we observed significant clinical benefit by gefitinib when used in higher lines of therapy, comparable to that in first- or second-line (15). Thus, we conclude that it is reasonable to initiate gefitinib in patients with favourable clinical features even if several lines of palliative treatment (Figure 2) have failed.

Furthermore, clinical observations shortly after initiation of gefitinib may provide a clue as to whether or not gefitinib therapy will be successful. Skin toxicity seems to be a class-specific side-effect of anti-EGFR therapy, and, as an example, in NSCLC it is well documented that with erlotinib treatment, skin toxicity was positively associated with disease control and prolonged PFS (20). Such an association has been less well described in gefitinib-treated NSCLC, but we assumed that appearance of rash closely correlated with superior CBR and survival (Table II and Figure 3). Therefore, the development of skin rash should be viewed as a valuable clinical indicator for response to gefitinib therapy. In our analysis, we qualified both acne-like rash, exanthema and PPE as skin toxicity, but were also able to observe that either of these skin side-effects of gefitinib therapy appeared to indicate a favourable therapeutic response (data not shown). These findings seem to be contradictory to earlier trials in which skin toxicity failed to be of predictive value. However, in those trials (18, 19), only higher grades of skin toxicity were included for statistical calculation, whereas in the present trial, even low grades were included.

As expected, we found that patients who responded or showed SD achieved a significantly better outcome than patients who experienced disease progression. Of note, patients in whom SD but no objective response was observed had PFS and OS no different from those with PR (Figure 3). Thus, from the clinician's point of view, disease control with SD by gefitinib seems to be associated with a profound benefit, a finding also reported by other investigators (15).

In conclusion, gefitinib resulted in a clinical benefit in a remarkable proportion of patients, and the outcome in the whole cohort and in subgroups (women, never-smokers) was closely comparable to that in published studies. Thus, our survey confirms efficacy of gefitinib in the routine setting. In our study, we highlighted that clinical parameters are good predictors for response to EGFR-TKI therapy, which is of value if *EGFR* mutation status is not available.

Conflict of Interest Statement

AP, EU and WS have no conflict of interest to disclose. WH served as a consultant and advisory board member and received an unrestricted scientific grant and honoraria from Astra Zeneca, Austria. MF, HJ, GP, and BZ received honoraria (lectures) from Astra Zeneca, Austria.

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