Original article

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Activity of a specific inhibitor, gefitinib (Iressa™, ZD1839), of epidermal growth factor receptor in refractory non-small-cell lung cancer

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Background: Gefitinib (Iressa™, ZD1839) is an orally active, selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. Phase I studies showed that it is well tolerated, with evidence of tumor regression in patients with advanced non-small-cell lung cancer (NSCLC). Therefore, we aimed to assess the antitumor activity and tolerability of gefitinib in a series of patients with previously treated, advanced NSCLC, as a part of a compassionate use program.

Patients and methods: To be eligible, all patients were required to have histologically or cytologically proven advanced or metastatic NSCLC, prior chemotherapy with at least one cisplatin-containing chemotherapy regimen or contraindication to cytotoxic drugs, Eastern Cooperative Oncology Group performance status ≤2, and adequate hematological, renal and hepatic parameters. All patients provided signed informed consent. Patient re-evaluation was performed every 4–6 weeks.

Results: Seventy-three consecutive patients were enrolled. Response rate, including complete and partial response, was 9.6%; an additional 43.8% of patients achieved stable disease, for an overall disease control of 53.4%. EGFR1 status was evaluated by immunocytochemistry in 25 patients. According to EGFR1 immunoreactivity all responses were observed with medium/strong imunoreactivity while three out of four responses were observed in high expressive patients. Median survival for all patients was 4 months while it reached 6 months for patients with disease control. The 1-year survival rate was 13.1% for the entire series and 23.2% for patients with disease control. Non-hematological toxicity was generally mild.

Conclusion: Gefitinib has promising activity with a good toxicity profile in patients with progressive NSCLC who have received one or two prior chemotherapy regimens. A possible relationship within response and EGFR1 expression is suggested.

Key words: epidermal growth factor receptor, gefitinib, non-small-cell lung cancer

Introduction

The epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases has emerged as an essential factor in the development and growth of many types of malignant tumors. These receptors are involved in a complex signal transduction cascade that modulates a network involved in tumorigenic processes like cancer-cell proliferation, adhesion, migration, differentiation, as well as protection from apoptosis [1–3].

The EGFR family comprises four distinct transmembrane receptors (EGFR/Erb B-1, HER 2/Erb B-2, HER 3/Erb B-3, and HER4/Erb B-4) composed of an extracellular ligand-binding domain and a cytoplasmic region with enzymatic activity. A number of different ligands, including EGF-like molecules, neuregulins and transforming growth-factor (TGF)-α, activate the receptor permitting the release of activated effector and adaptor proteins into the cytoplasm where they stimulate many different signal transduction cascades, such as the mitogen-activated protein kinase pathway, the anti-apoptotic kinase Akt, phosphoinositol kinase and several transcriptional regulators [4–7].

It has been well demonstrated that the aberrant activity of EGFR signalling plays a key role in the development of tumor cell growth. In particular, growth factor receptors are overexpressed in a variety of common solid tumors, including non-small-cell lung, head and neck, colorectal, pancreatic, renal and ovarian cancer [8–10]. Increased EGFR expression is therefore likely to be a strong prognostic indicator in various tumor types [11] and its inhibition by agents designed to target these specific molecular processes seems to induce substantial therapeutic benefits [12, 13].

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One of the most important milestones in the development of these novel antitumor agents was the concept of therapy based on the inhibition of the EGFR.

Gefitinib (Iressa™, ZD1839) is an orally active, selective EGFR tyrosine kinase inhibitor that blocks signal transduction pathways implicated in cancer growth [4, 10]. Phase I studies showed gefitinib to be generally well tolerated with evidence of tumor regression and disease stabilization in patients with advanced non-small-cell lung cancer (NSCLC) [14, 15]. Two large phase II studies seem to indicate clinically meaningful antitumor activity and symptom relief in patients with advanced NSCLC who had received prior chemotherapy [16, 17]. We aimed to assess the antitumor activity and tolerability of gefitinib in a series of patients with previously treated, advanced NSCLC, as part of a compassionate use program.

Patients and methods

To be eligible for gefitinib therapy, all patients must have received prior chemotherapy with at least one cisplatin-containing chemotherapy regimen. Untreated patients with medical contraindication to cytotoxic drugs and those who refused second-line chemotherapy were also included. Previous radiotherapy was not an exclusion criterion. All patients were required to have histologically or cytologically proven advanced or metastatic NSCLC as well as at least one measurable lesion. Patients with brain metastases were excluded only if symptomatic. Each patient was required to have performance status ≤2 on the Eastern Cooperative Oncology Group (ECOG) scale and adequate hematological, renal and hepatic parameters. To be included, at least 30 days must have elapsed from the last chemotherapy regimen. Although the study drug was given on a named-patient basis, all patients provided signed informed consent.

Study design

Before starting gefitinib treatment, all patients underwent a complete medical history and physical examination. Additionally, in all patients complete hematological and biochemical testing was carried out as well as electocardiogram and baseline chest X-ray. Assessment of disease extent was performed with complete tomographic scans (CT) of thorax and upper abdomen. Brain CT scan was carried out in case of suspicious neurological symptoms of metastases. A radionuclide bone scan was performed when clinically required. Patients were re-evaluated every 6 weeks with regard to response as well as to toxicity. Both CT scan and assessment of other parameters of disease were repeated every 6 weeks and treatment was continued until disease progression and/or unacceptable toxicity.

Gefitinib was supplied by AstraZeneca on a named patient basis in tablets of 250 mg, which constitutes the daily treatment dose. Patients were not selected by tumor EGFR status.

The primary aim of this analysis was to evaluate the objective tumor response (complete plus partial response) rate, disease control (objective response plus stable disease) rate, and safety profile of gefitinib at 250 mg/day in patients with previously treated NSCLC. Secondary aims were to evaluate survival and to correlate EGFR1 tumor status with response to gefitinib.

Assessment of response and toxicity

Objective tumor response and its duration were assessed according to RECIST response criteria [18] and all responses had to be confirmed ≥30 days after the initial assessment of response. Time to disease progression was calculated from the date of start of therapy until the date of disease progression. Survival was assessed from the first dose of gefitinib until the date of death. All patients were evaluated in an intent-to-treat analysis. Toxicity was recorded according to the NCI Common Toxicity Criteria 2.0.

Table 1. Patient characteristics

Characteristics	No. of patients	%
Evaluable patients	73	100
Males/females	57/16	78/22
Median age in years (range)	63 (32–76)	
Performance status		
0	10	13.7
1	48	65.8
2	15	20.5
Histology		
Adenocarcinoma	39	53.4
Squamous cell	17	23.3
Other	17	23.3
No. of previous chemotherapy regimens		
0	5	6.8
1	28	38.4
≥2	40[a]	54.8
Best response to prior chemotherapy		
Complete/partial	26	35.6
Stable	21	28.8
Progression	16	21.9
Not evaluable	10	13.7

[a]Five patients pretreated with three chemotherapy lines.

Assessment of EGFR immunoreactivity

EGFR1 status was evaluated by immunocytochemistry carried out using the MoAb EGFrAb-10 (clone 111.6), neomarkers (Union City, CA, USA) diluted 1:100 and revealed by the En Vision detection system (Dako, Glostrup, Denmark). Normal skin, placenta and liver were used as normal control. Only membrane immunoreactivity was considered. The percentage of neoplastic cells showing membranous immunoreactivity was semiquantitatively evaluated (range 0–100%). Cases showing 0–19% immunoreactive cells were considered negative/low expressors while cases showing ≥20% immunoreactive cells were considered high expressors.

The staining intensity of immunoreactive cells was also scored as negative to faint (0/1+) or medium to strong (2+/3+).

Results

From February 2001 to February 2002, 73 consecutive patients with advanced NSCLC were enrolled on the study. The baseline patient characteristics are summarized in Table 1. The majority of patients were male (78%) and had an ECOG performance status <2 (79.5%). Median age was 63 years (range 32–76 years). Adenocarcinoma was the most frequent histological subtype (53.4%). All patients but five were pretreated with one (28 cases), two (35

Table 2. Response rate and disease control rate of gefitinib according to patient characteristics

	Responses				Disease control		
	No. of patients	No. of responses	%	95% CI	No. of patients	%	95% CI
Total	73	7	9.6	3.9–18.7	39	53.4	41.3–65.2
Prior chemotherapy							
≤1	37	3	8.1	1.7–21.9	21	56.7	39.4–72.9
≥2	36	4	11.1	3.1–26.0	18	50	36.92–67.08
Histology							
Adenocarcinoma	39	6	15.3	5.8–30.5	23	58.9	42.1–74.4
Squamous cell	17	1	5.8	0.1–28.6	7	41.1	18.4–67.0
Other	17	0	0	0–19.5	9	52.9	27.8–77.0
Performance status							
≤1	58	6	10.3	3.8–21.1	35	60.3	46.6–72.9
2	15	1	6.6	0.1–31.9	4	26.6	7.7–55.1
Previous response to chemotherapy							
CR + PR	26	2	7.6	0.9–25.1	12	46.1	26.5–66.6
SD	21	2	9.5	1.1–30.3	13	61.9	38.4–81.8
PD	16	2	12.5	1.5–38.3	8	50	24.6–75.3
NA	10	1	10	0.2–44.5	6	60	26.2–87.8

CI, confidence interval; CR, complete response; NA, not available; PD, progressive disease; PR, partial response.

Table 3. Time to disease progression and overall survival related to response

	All patients (73 patients)	CR + PR (7 patients)	SD (32 patients)	Disease control (39 patients)
Time to disease progression				
Median, months (range)	3 (0–16+)	4 (3–7+)	4 (2–16+)	4 (2–16+)
Median survival, months (range)	4 (0–17+)	6 (4–11+)	6 (3–17+)	6 (2–17+)
Overall survival (%)				
At 6 months	31.2	57.1	49.1	50.6
At 12 months	13.1	NE	21.4	23.2

CR, complete response, NE, not evaluable, PR, partial response, SD, stable disease.

cases) or three (five cases) chemotherapy regimens. All pretreated patients received one platinum-containing regimen. One patient refused chemotherapy. The causes of exclusion for those patients unable to receive prior chemotherapy were: ischemic cardiomyopathy in two patients, age 78 years with low performance status in one patient, and liver cirrhosis with thrombocytopenia in one patient, respectively. With regard to best response to prior chemotherapy, 35.6% had achieved complete or partial response, 28.8% stable disease, 21.9% progression, while the remaining 13.7% were not evaluable.

Table 4. Toxicities recorded during treatment in 73 patients

Toxicity	Grade 1–2	Grade 3
	No. of patients (%)	No. of patients (%)
Skin rash	51 (70)	4 (5)
Diarrhea	31 (42)	1 (1)
Nausea	7 (10)	0 (0)

Response and survival

In the intention-to-treat analysis of response rates, all patients were included whether or not the response could be properly evaluated. The response rate was 9.6%, including complete (one) and partial (six) responses; an additional 43.8% of patients achieved stable disease, for an overall disease control of 53.4%. Median duration of response was 4 months (range 2–7 months). The likelihood of achieving a response as well as disease control

Table 5. Responses to gefitinib according to EGFR1 expressed as staining intensity or percentage of immunoreactive cells in 25 patients

	No. of patients	Responses			Stable disease			*P* value
		No.	%	95% CI	No.	%	95% CI	
Total	25	4	16	4.5–36.8	11	44	24.4–65.0	NS
Staining intensity								
2+/3+	14	4	28.6	8.3–58.1	3	21.4	4.6–50.8	NS
0/1+	11	0	0	0–28.4	8	72.7	39.0–93.8	NS
Percentage of immunoreactive cells								
High expressors	9	3	33.3	7.4–70.0	2	22.3	2.8–60.0	NS
Negative/low expressors	16	1	6.3	0.1–30.2	9	56.2	29.8–80.2	NS

High expressors, ≥20%; negative/low expressors, 0–19%.
CI, confidence interval; NS, not statistically significant.

was not influenced by the main pretreatment characteristics (Table 2). In particular, the number of prior chemotherapy regimens, histology and best response to prior chemotherapy did not modify the incidence of response rate to gefitinib, neither did gender (three of 16 females and four of 57 males). All responses were observed after 1 month; one patient with lung metastases achieved complete remission lasting >3 months, while a partial response was observed in a patient with brain metastases. With a median follow-up of 4 months, the median survival for all series was 4 months while it reached 6 months for the 39 patients with disease control. The 1-year survival rate was 13.1% for the entire series and 23.2% for patients with disease control (Table 3).

Toxicity evaluation and treatment compliance

All patients were evaluated for toxicity. Non-hematological toxicity was mild as listed in Table 4. Grade 1/2 and grade 3 skin rash were observed in 70% and 5% of patients, respectively. One patient presented with grade 3 diarrhea that required gefitinib interruption for 1 week and then intermittent administration of drug. Hematological toxicity was not observed. No interstitial drug-related lung disease was observed.

All patients but one received gefitinib at the planned dose until progression. One patient received gefitinib 250 mg every other day after grade 3 diarrhea with benefit. To date, two stable disease patients are still on treatment with 250 mg every day at 29 and 18 months from starting gefitinib.

EGFR immunoreactivity and response

EGFR1 analysis was performed in tumor specimens available from 25 patients included in this study (Table 5). According to staining intensity, 14 and 11 patients had, respectively, medium/strong and negative/faint immunoreactivity, while, according to percentage immunoreactive cells, nine and 16 patients had high and low/negative expressors, respectively. Four patients achieved partial remission, 11 stable disease and 10 progressive disease. All responses were observed in patients with medium/strong immunoreactivity while three out of four responses were observed in high expressor patients.

Discussion

The outcome of patients with NSCLC failing or progressing after first-line chemotherapy is poor [18]. Recently, docetaxel has been studied extensively with a response rate ranging from 14% to 24% in seven phase II trials, involving more than 300 patients [19]. These promising phase II studies led to two randomized trials, both demonstrating the advantage of docetaxel versus either vinorelbine or ifosfamide [20] as well as the best supportive therapy [21]. However, the overall response rate after docetaxel was ~6.7%. Despite this low response rate, treatment with docetaxel resulted in a significant prolongation of median survival (7.5 months) with a 1-year survival of 37% when this drug was given at a dose of 75 mg/m^2 every 3 weeks [21].

Following these trials, docetaxel at 75 mg/m^2 every 3 weeks has been considered as the gold standard for patients with NSCLC who have previously been treated with a first-line platinum-based regimen. Nonetheless, from these results it appears clear that new approaches are required to further improve the outcome of patients with NSCLC [22].

Apart from prevention, screening and early detection, novel treatments based on a better understanding of the molecular mechanisms of this disease could change the long-term expectations for patients with NSCLC. From this viewpoint, the development of EGFR tyrosine kinase inhibitors currently represents the most appealing biological approach for NSCLC [6, 12, 23]. The preliminary results of randomized [16, 17] and non-randomized [24–26] studies reported response rates ranging from 0 to 18.4%, disease control rates of 26.6–54.4% and median survival of 4.2–8.1 months. Some differences in the results could be explained by different patient selection; for example, in the two IDEAL studies gefitinib was administered to patients who had received at least one (IDEAL 1) or at least two (IDEAL 2) prior chemotherapy regimens [16, 17].

In our series we reported a response rate of 9.6% and a disease control rate of 53.4% with a median overall survival of 4 months. However, a major concern has been the observation that all responses were observed in patients with high expression of EGFR or medium/strong immunoreactivity (Table 5). This issue

deserves further evaluation in larger series on both clinical and biological basis.

Our results are in agreement with the two major randomized phase II studies with gefitinib and strongly support the use of this drug as second- or third-line treatment of advanced NSCLC. Additionally, the good toxicity profile of this drug, mainly consisting of mild skin reactions, further supports an adequate clinical-benefit evaluation versus docetaxel as standard treatment for patients refractory to first-line therapy.

Recently, the results of two randomized trials comparing chemotherapy alone versus chemotherapy plus gefitinib [27, 28] failed to demonstrate any advantage in response rate, progression-free survival, time to worsening of symptoms or overall survival. Yet it is likely that only a subset of NSCLC patients should be sensitive to EGFR inhibitors. Obviously the level of EGFR expression in the tumor could be the mainstep in evaluating the EGFR inhibitors as well as the network of interactions at the ligand, receptor and downstream signaling levels [12, 29]. Another important unsolved issue could be represented by the definition of the best administration schedule, i.e. intermittent versus continuous, as well as the optimal combination with chemotherapy.

Thus, well-designed randomized trials are required to determine the role of gefitinib as first- as well as second-line treatment, alone or in combination with chemotherapy. Additionally, its role as adjuvant therapy as well as maintenance should be investigated. In the meantime, after decades of nonselective and nonspecific chemotherapy regimens, we can hope for a real improvement in NSCLC outcome with the introduction of specific, selective and non-toxic biological drugs.

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