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Clinical benefit in NSCLC: the evidence for gefitinib (‘Iressa’, ZD1839)

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Abstract

In recent years it has become widely recognised that clinical benefit in cancer patients depends on factors such as symptom improvement, symptom-free survival and low toxicity, as well as the more conventional measures of tumour regression and improved overall survival. Advanced non-small-cell lung cancer (NSCLC) is a debilitating disease, the prognosis for which has improved very little over the past few decades. There is therefore a clear need for alternative options for the treatment of advanced NSCLC. The epidermal growth factor receptor tyrosine kinase inhibitor gefitinib (‘Iressa’, ZD1839) has been in use in clinical trials for several years. The clinical benefit it provides in patients with advanced NSCLC is a product of the notable antitumour activity, high rates of symptom improvement and favourable tolerability profile.

Keywords: Gefitinib; Iressa; ZD1839; Clinical benefit; Epidermal growth factor receptor; EGFR

1. Introduction – what is clinical benefit?

A number of different factors must be taken into account when assessing the clinical benefits of a given anticancer drug. Arguably the most common factors that are understood to contribute to clinical benefit are objective measures of response, such as tumour regression or decline in a tumour marker. However, it does not necessarily follow that such changes have a meaningful impact on a patient’s well-being or overall quality of life (QoL). In fact, given that many of the chemotherapeutic agents that result in outcomes such as tumour regression are also associated with significant toxicity, it may well be that treatment with such agents can result in an overall negative impact on QoL. It is therefore important to recognise that factors such as symptom improvement, symptom-free survival and low toxicity, in addition to the more conventional measures of tumour regression and improved overall survival, are all key desired outcomes of cancer treatment that contribute to clinical benefit.

Advanced non-small-cell lung cancer (NSCLC) is a debilitating disease, the prognosis for which has improved very little over the past few decades. In a phase III study, comparing three experimental first-line platinum-based chemotherapy regimens to the standard regimen (cisplatin plus paclitaxel), there was no significant difference in response rates (19%) or median survival (8 months) between the four regimens [1]. The combination of gemcitabine and cisplatin did show a significantly longer time to disease progression than the standard regimen, but was also associated with an increased risk of renal toxicity, and the prolonged time to progression did not result in improved survival. When patients receive subsequent cycles of chemotherapy, the prognosis and outcome are even more challenging. A retrospective analysis of patients with NSCLC who had received three or four chemotherapy regimens demonstrated that response rates dropped with each line of chemotherapy, from 21% for those receiving first-line therapy to 0% for patients receiving fourth-line therapy [2]. There is therefore a clear need for alternative options for the treatment of advanced NSCLC.

The epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) gefitinib (‘Iressa’, ZD1839) entered clinical trials in 1997. Since that time, a number of important phase I, II and III studies have been conducted using gefitinib, which confirm clinical benefit in patients with NSCLC.

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2. Gefitinib monotherapy has antitumour activity against NSCLC

Initially, gefitinib exhibited encouraging antitumour activity (partial tumour response or disease stabilisation) in patients with advanced NSCLC in four open-label, multicentre, phase I dose-escalation studies involving patients with a variety of solid malignant tumours [3–6]. Responses were seen across the dose range of 150–700 mg/day, with no clear dose-response relationship (Table 1). Furthermore, over 20% of NSCLC patients remained on study for ≥3 months, including eight patients who received gefitinib for over a year.

These encouraging results were confirmed by two large, double-blind, phase II trials, IDEAL 1 and 2 ('Iressa' Dose Evaluation in Advanced Lung Cancer), initiated to investigate gefitinib monotherapy in pretreated patients with advanced NSCLC [7,8]. Fixed doses of 250 and 500 mg/day were selected for investigation, as 250 mg/day is higher than the lowest dose level at which objective tumour regression was seen, while 500 mg/day is the highest dose that was well tolerated when taken chronically in phase I trials. In IDEAL 1, patients had received one or two prior chemotherapy regimens (at least one platinum based), and in IDEAL 2, patients had received at least two prior chemotherapy regimens, including platinum and docetaxel, either concurrently or separately.

In these two studies, gefitinib 250 mg/day was as effective as, and better tolerated than, 500 mg/day, and is therefore the recommended dose in this clinical setting. At this dose, disease control rates (response + stable disease) were 54.4 and 42.2%, while the objective radiographic response rates were 18.4 and 11.8% in IDEAL 1 and 2, respectively. The difference in efficacy between the two trials was expected, as patients in IDEAL 1 had a better prognosis than those in IDEAL 2 and had been exposed to fewer chemotherapy regimens. Most notable of the response to gefitinib is the speed of onset. Of the patients who responded, most showed rapid tumour regression, with the majority (77%) meeting the criteria for objective response by the first post-baseline assessment. Disease control and objective tumour responses were seen, regardless of the number of prior chemotherapy regimens, in both trials (Fig. 1).

Table 1
Number of NSCLC patients showing partial response or stable disease in phase I trials of gefitinib. Reproduced with permission from: Herbst RS, Kies MS. ZD1839 (Iressa™) in non-small cell lung cancer. *Oncologist* 2002, **7 (Suppl 4)**, 9–15

Geftinib dose [a] (mg/day)	Partial response (*n*)	Stable disease (*n*)
50 ($n = 4$)	0	1
100 ($n = 4$)	0	0
150 ($n = 13$)	1	1
225 ($n = 17$)	1	3
300 ($n = 16$)	1	2
400 ($n = 13$)	2	2
525 ($n = 11$)	3	1
600 ($n = 4$)	0	1
700 ($n = 6$)	2	0
800 ($n = 5$)	0	1
1000 ($n = 7$)	0	1

[a] Twenty-four of these patients were on an intermittent dosing schedule; 14 days on, 14 days off gefitinib

Gefitinib was made available on a compassionate-use basis to patients with advanced NSCLC who had no other treatment options. By June 2003, >37,000 patients had received gefitinib 250 mg/day monotherapy as part of this global Expanded Access Programme (EAP). The majority have received and failed chemotherapy for advanced incurable stage III/IV NSCLC, while a small minority are chemonaive patients for whom no other treatment options are available, due to comorbidity or poor performance status. A number of reports from individual institutions participating in the EAP support the antitumour activity of gefitinib monotherapy in this setting. The overall disease control rate from several reports comprising 456 evaluable patients is >40% [9–13], which is consistent with the findings of clinical trials.

3. Survival data for gefitinib monotherapy are encouraging

In IDEAL 1 and 2 [7,8], overall median survival times for the 250 mg/day dose were 7.6 and 6.5 months, respectively (Fig. 2), while one-year survival rates were 35 and 29%, respectively. These data are very encouraging for this patient population and compare favourably with data from a retrospective analysis, which showed a median overall survival time of 4 months and a one-year survival rate of only 5.5% for a similar group of patients [2]. Interestingly, median survival rates in patients with an objective tumour response were 13.3 and 17.9 months in IDEAL 1 and 2, respectively.

An *ad hoc* retrospective analysis was performed on survival data from patients who received gefitinib as part of the EAP. Duration of survival was measured from the start of initial treatment or earliest gefitinib resupply date (if date of initial treatment was unavailable) to the last resupply date for ongoing patients or the date of last dose for patients who withdrew from the programme. Evaluable patients ($n = 17{,}152$) had entered the EAP in the United States at least one year prior to the analysis and showed a median survival of 5.8 months and a one-year survival rate of 33% [14]. This further confirms that data from the EAP are comparable to those obtained from pretreated patients with advanced NSCLC in the phase II IDEAL 1 and 2 trials. The one-year survival rate in the EAP is comparable to that of docetaxel in pretreated patients (32–37%) [15,16].

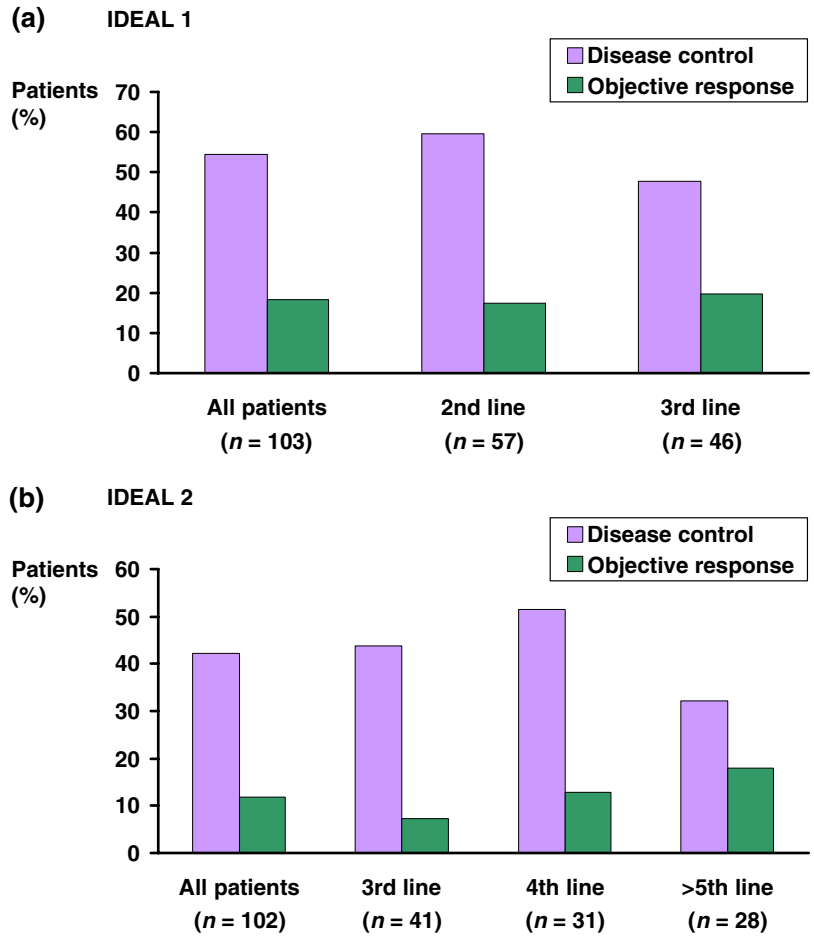

Fig. 1. Objective response and disease control by the number of prior chemotherapy regimens in IDEAL 1 (a) and 2 (b).

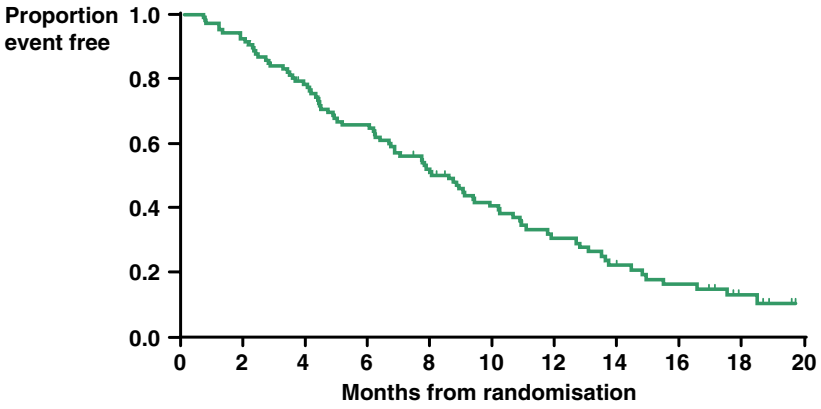

Fig. 2. Kaplan-Meier curves showing overall survival in IDEAL 1 (250 mg/day). Reproduced with permission from: Fukuoka M, Yano S, Giaccone G, *et al*. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2003, **21**, 2237–2246. Reprinted with permission from the American Society of Clinical Oncology.

4. Gefitinib monotherapy provides symptom improvement and QoL benefits

Patients with advanced NSCLC often suffer from a range of distressing and debilitating symptoms, therefore any discussion of clinical benefit must address amelioration of these disease-related symptoms. In the phase I gefitinib monotherapy studies, there was some anecdotal evidence of symptomatic control or improvement with gefitinib; some patients noted a reduction in pain and dyspnoea, which returned within 3 days of cessation of gefitinib therapy on an intermittent schedule. Functional Assessment of Cancer Therapy (FACT) questionnaires were used as an exploratory endpoint to investigate QoL

in these phase I studies. In patients with NSCLC or head and neck cancer, median FACT scores did not deteriorate significantly. In patients with NSCLC, symptom-related scores measured by the Lung Cancer Subscale of FACT-L appeared sensitive to clinical change [17]. Many patients in IDEAL 1 and 2 reported improvements in disease-related symptoms and QoL, and symptom improvement rates were 40.3 and 43.1%, respectively. The effect of gefitinib on symptom improvement and QoL is reviewed in depth by Peter G Harper (this volume).

5. Gefitinib in combination with chemotherapy – a learning point

Due to the significant antitumour activity of gefitinib when given alone to pretreated patients with advanced NSCLC [7,8] and the additive or synergistic activities of gefitinib and several chemotherapeutic drugs seen in preclinical models [18], the oncology community was optimistic that combination of gefitinib with standard chemotherapy agents would provide clinical benefit over chemotherapy alone in patients with advanced NSCLC. Furthermore, two phase I studies, in which gefitinib was combined with the chemotherapy regimens later used in INTACT 1 and 2 ('Iressa' NSCLC Trials Assessing Combination Treatment), demonstrated that these combinations were feasible, well tolerated and showed encouraging antitumour activity [19,20].

However, in two prospective, phase III, placebo-controlled randomised studies (INTACT 1 and 2) that investigated gefitinib combined with six cycles of chemotherapy (INTACT 1 = gemcitabine/cisplatin; INTACT 2 = carboplatin/paclitaxel) followed by gefitinib/placebo monotherapy in advanced, previously untreated NSCLC [21,22], the addition of gefitinib (250 or 500 mg/day) to chemotherapy did not provide a survival advantage over chemotherapy alone in chemonaive patients. Response rate and median time to progression were not improved with gefitinib. The reason for these disappointing results is still not clear. The trials were robust and well balanced with respect to all baseline and patient characteristics. It could be that each of the agents is working against the same population of susceptible tumour cells, making the effect redundant rather than additive. Alternatively, it may be that sequencing is critical in the interaction of gefitinib and chemotherapy.

Interestingly, however, in the time-to-progression curves for INTACT 2, the decline in the placebo curve increases at approximately 6 months after randomisation, while the two gefitinib curves continue their steady decline (Fig. 3). A similar but less marked effect was seen in INTACT 1. This suggests that gefitinib might be maintaining the response when chemotherapy has been terminated, and consequently that the best use of gefitinib *in vivo* could be in sequence with chemotherapy. However, there is no statistically significant result from the INTACT studies to support this, so further clinical trials will be needed to clarify this issue of sequencing. A phase III study is already underway to compare gefitinib 250 mg/day with placebo following chemoradiation and consolidation docetaxel in patients with inoperable stage IIIA/B NSCLC. A number of other studies are also planned or underway to further elucidate the potential benefits of gefitinib 250 mg/day in a range of clinical settings, including in combination with platinum-based chemotherapy in tumours other than lung cancer.

6. Gefitinib has a well-established safety and tolerability profile

Gefitinib showed acceptable tolerability in the phase I studies [3–6]. The maximum tolerated dose was

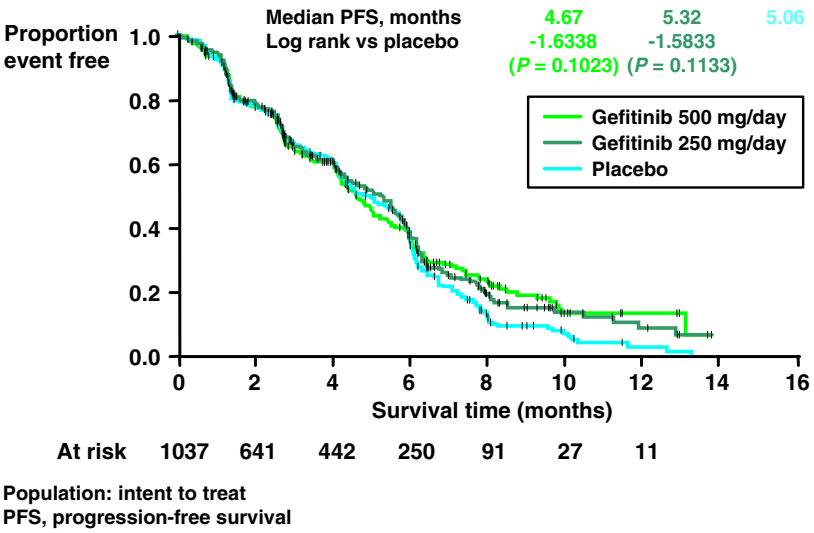

Fig. 3. Time-to-progression curve in INTACT 2.

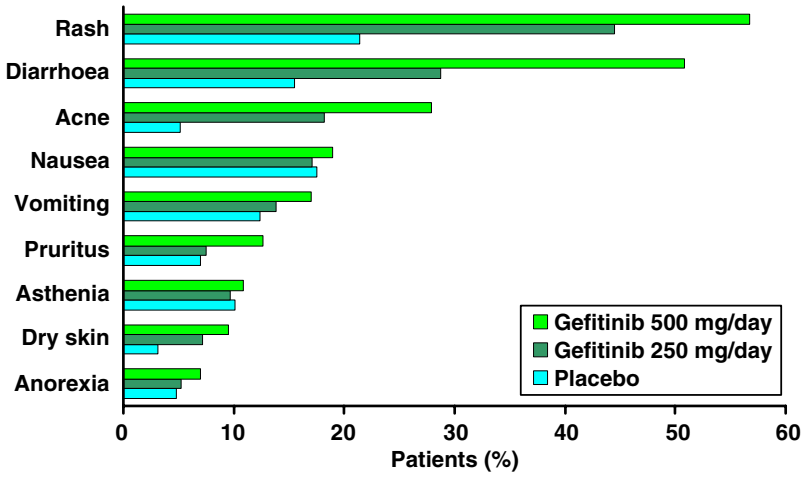

Fig. 4. Commonly occurring gefitinib/placebo-related adverse events in INTACT 1.

≥700 mg/day, with a predominant dose-limiting toxicity of diarrhoea. The most common adverse drug reactions (ADRs) seen in these trials were gastrointestinal (diarrhoea, nausea, vomiting) or skin reactions (rash, acne, dry skin, pruritus), all seen in >10% of patients, and asthenia and increased transaminases, seen in 5–10% of patients. Most of these adverse events (AEs) were mild (National Cancer Institute Common Toxicity Criteria grade 1 or 2) and generally resolved during the treatment period, following temporary treatment interruption or upon cessation of gefitinib therapy. Significantly, common chemotherapy-associated toxicities such as neuropathy, myelosuppression, neutropenia or other haematological toxicities were not observed. The frequency and severity of most ADRs were dose related. In patients receiving >525 mg/day gefitinib, higher incidences of grade 3 or 4 ADRs and ADRs leading to withdrawal were seen compared with patients receiving ≤500 mg/day. Few patients required a dose reduction (7%) or interruption (7%) as a result of ADRs, and for those who did, the majority (74%) had received gefitinib at a dose of ≥600 mg/day.

Similarly, in the phase II IDEAL 1 and 2 studies, the most common ADRs were mild (grade 1/2), non-cumulative, dose-related skin reactions and diarrhoea. No unexpected ADRs or characteristic chemotherapy side effects were observed with gefitinib. Patients receiving 500 mg/day had a higher incidence of grade 3 or 4 ADRs than those receiving 250 mg/day, with this increased incidence mostly being accounted for by diarrhoea and skin toxicity. Withdrawal rates due to drug-related AEs at the recommended 250 mg/day dose were 1–2%, and <1% of patients required dose reductions due to ADRs.

The favourable safety profile of gefitinib was further confirmed in the placebo-controlled phase III studies, INTACT 1 and 2. The most commonly occurring AEs were gastrointestinal, skin-related or haematological in nature. AEs were observed in a similar proportion of patients in each of the treatment groups, with the exception of diarrhoea and skin reactions, which are known to be associated with gefitinib treatment (Fig. 4). At the 250 mg/day dose, <1.5% of patients were withdrawn due to diarrhoea or skin reactions.

Recent reports from Japan have questioned the association of gefitinib with interstitial lung disease (ILD) [23]. ILD, including interstitial pneumonia, is a known complication of lung cancer, irrespective of treatment, while smoking and infection are also significant risk factors. Furthermore, it is well accepted that ILD is associated with other cancer treatments, with incidences of up to 6% for standard chemotherapy agents [24] and around 7% for radiotherapy [25]. Patients receiving gefitinib have often been previously treated with one or more of these therapies. In around 80,000 patients worldwide who have received gefitinib, the reported incidence of ILD is approximately 1%, and approximately 0.35% in an extensive worldwide compassionate-use programme of gefitinib involving nearly 38,500 patients. The global data are consistent with the results from INTACT 1 and 2, in which the incidence of ILD was similar in the placebo and gefitinib groups. Interestingly, the reported incidence of ILD is around six times higher in Japan than in the rest of the world. It is possible that this difference may be due to pharmacogenomic factors; however, further study is needed to understand the reasons for this apparent difference.

7. Conclusions

The combined data from clinical trials and the EAP demonstrate that the recommended 250 mg/day dose of gefitinib monotherapy provides evidence of symptom improvement in >40% of patients who have no other treatment options. Between 10 and 19% of patients treated with this agent experience a clinically meaningful response. The tolerability profile of gefitinib is favourable and well established through wide clinical experience; the most common AEs are mild, reversible gastrointestinal and skin

disorders and gefitinib is not typically associated with characteristic chemotherapy side effects such as haematological toxicities. In this area of high unmet clinical need, gefitinib has a favourable risk/benefit ratio, making gefitinib a very reasonable treatment alternative for these patients for whom no other proven effective treatment exists.

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