Development of the Novel Biologically Targeted Anticancer Agent Gefitinib: Determining the Optimum Dose for Clinical Efficacy

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ABSTRACT

The emergence of novel, biologically targeted anticancer agents such as gefitinib (‘Iressa’, ZD1839) has raised the question of how the dose for later-stage clinical development and clinical use is best determined. For cytotoxic drugs, because toxic effects and antitumor activity often fall within the same dose range and are dose dependent, the clinically used dose will depend on the therapeutic window. Therefore, the maximum tolerated dose identified in Phase I trials is typically used to determine the dose level for Phase II and III trials. However, because biologically targeted agents are expected to provide clinical benefits that are not predicted by surrogate end points of toxicity to normal replicating tissue, new Phase I trials have been designed to determine the optimum biological dose for use in further studies.

A large, multifaceted Phase I program was designed to evaluate the pharmacokinetics, safety, efficacy, and targeted biological activity of a once-daily oral dose of gefitinib. The maximum tolerated dose was ≥700 mg/day, although doses as low as 150 mg/day provided (a) plasma concentrations sufficient for pharmacological activity, (b) evidence of targeted biological effect, and (c) antitumor activity. From these observations, two large Phase II trials (‘Iressa’ Dose Evaluation in Advanced Lung Cancer 1 and 2) evaluated 250- and 500-mg/day doses of gefitinib in patients with advanced non-small cell lung cancer (NSCLC). As predicted from the Phase I trials, doses >250 mg/day provided no additional efficacy benefit, whereas adverse effects increased in a dose-dependent manner. Consequently, the recommended dose of gefitinib in NSCLC is 250 mg/day. The early clinical trial development of gefitinib provides a model for the development of novel, noncytotoxic anticancer agents.

INTRODUCTION

In recent years, the search for novel anticancer agents has moved from cytotoxic agents to biologically targeted agents (which are primarily antiproliferative) to avoid the traditional toxic effects of anticancer therapy and to develop more selective and effective agents. Traditionally, Phase I trials of anticancer agents aim to identify toxicities, pharmacokinetic (PK) profiles, and the dose for Phase II trials. For cytotoxic agents, antitumor activity and toxic effects generally occur within a similar dose range, and the dose selected is usually the maximum tolerated dose (MTD; Fig. 1A; Ref. 1). However, for biologically targeted agents that are cytostatic, the maximum biological effect may occur at doses lower than the MTD (Fig. 1B) and alternative end points based on biological and/or clinical activity rather than toxicity might be more appropriate (2). Alternative end points may include changes in tumor markers, prolonged disease stabilization, improvements in disease-related symptoms, pharmacodynamic assessment of the biological activity of the target molecule, and pharmacokinetic studies.

One promising biological target is the epidermal growth factor receptor (EGFR), because EGFR activation initiates a signaling cascade that leads to a number of processes involved in tumor progression, including increased proliferation, angiogenesis and invasion, and decreased apoptosis (3). In addition, a variety of tumors express EGFR (4), giving rise to the wide application of EGFR-targeted agents such as gefitinib (‘Iressa,’ ZD1839), an EGFR tyrosine kinase inhibitor. This review will discuss how the strategic aim of defining the optimum biological dose (OBD) of gefitinib in the early clinical trial program was achieved.

DESIGNING A CLINICAL TRIAL FOR GEFITINIB

Several challenges were present in designing the Phase I clinical trials of gefitinib, because this agent was expected to be cytostatic rather than cytotoxic; hence, objective tumor responses might not be expected. These challenges included a scarcity of precedents, the way in which “biological activity” was defined, the integration of outcomes across multiple tumor types in Phase I trials (because the OBD and clinical activity may not necessarily be the same for all tumor types), the relationship between biological activity and clinical outcome, and unknown PK and pharmacodynamic (PD) relationships. Thus, four large, multicenter, randomized, oncology-like and clinical pharmacology-like Phase I trials were designed.

Two conventional oncology-like Phase I trials used dose escalation to identify the MTD and characterize the PK of gefitinib in patients; these trials also ascertained whether there was any evidence of antitumor activity (objective tumor response and stable disease). Two more sophisticated pharmacology-like Phase I trials were split into Part A (dose escalation) and Part B (randomized dose response). Up to four doses from Part A were to be evaluated in Part B, with alternative efficacy
end points to collate tumor-specific PK/PD data for each patient (tumor measurements, serum tumor markers, baseline and day-28 tumor EGFR levels, and cell proliferation indices from skin and tumor biopsies, where available). Data from these four trials would enable dose levels for the Phase II/III trials to be determined.

If a single dose level for Phase II/III trials could not be determined, a blinded-review panel would assess evaluable cases using the collated PK/PD data available from Part B of the two pharmacology-like Phase I trials. The relevance of the data (magnitude of change, reliability, and methodology) would be weighed in a prospective algorithm to assign an overall targeted biological effect (TBE) outcome (yes/no). Regression analysis from dose-response (for the TBE) and exposure-response relationships would be constructed, from which dose selection could be derived. Evidence of TBE would be based on tumor shrinkage, changes in tumor EGFR-specific markers [EGFR expression, phosphorylated EGFR, phospho-p44/42 mitogen-activated protein kinase (pMAPK)], proliferation (Ki67) or apoptosis, and skin EGFR markers and serum tumor markers.

**PHASE I TRIALS OF GEFITINIB**

Initial Phase I trials performed in healthy volunteers showed that oral administration of gefitinib given once on day 1 (50, 100, 250 or 500 mg) or daily for 14 days (100 mg/day) was feasible, and that PK parameters that were used to assess exposure to gefitinib increased in proportion to dose (5). Four multicenter Phase I trials then evaluated the safety profile of gefitinib (50–1000 mg/day) in more than 250 patients with a wide range of solid tumors that were known to express EGFR [e.g., non-small cell lung cancer (NSCLC) and head and neck, breast, colorectal, prostate, and ovarian cancers], although baseline expression levels were not determined (6–9). All of the patients had histologically confirmed advanced or metastatic tumors that were refractory to conventional chemotherapy or hormone therapy, were aged ≥18 years, and had a life expectancy of ≥12 weeks and a WHO performance status of 0–1.

**Oncology-like Trials.** Two conventional oncology-like Phase I monotherapy trials evaluated the safety of gefitinib (50–1000 mg/day) given daily for 14 days in 95 patients, followed by 14 days' observation (6, 7). Adverse events (AEs) occurred at doses ≥50 mg/day, with the most commonly reported AEs being mild-to-moderate (grade 1–2) acne-like rash, diarrhea, nausea, anorexia, vomiting, and asthenia. The frequency of AEs such as skin rash and diarrhea increased with dose, and the MTD was identified as 700 mg/day. Exposure to gefitinib increased with dose; in patients taking 100–700 mg/day, \( C_{\text{max}} \) (peak plasma concentrations) and \( \text{AUC}_{0–24} \) (area under the curve from 0 to 24 h) increased from 105 to 2146 ng/ml and 1860 to 36077 ng·h/ml, respectively. Despite a 6–8-fold interpatient variability at each dose level, biologically relevant plasma concentrations (>100 ng/ml, equivalent to the \( \text{in vitro IC}_{50} \) (inhibitory concentration) for KB oral carcinoma cells (3)) were generally maintained at doses >100 mg/day across the 24-h dosing period. Disease control in these trials was observed across the whole dose range; objective responses in 9 patients with NSCLC were seen at 225 mg/day, 300 mg/day, 400 mg/day, 525 mg/day, and 700 mg/day; and stable disease in 15 patients (5 with NSCLC) was seen at 50 mg/day, 100 mg/day, 225 mg/day, 400 mg/day, 525 mg/day, and 700 mg/day (6, 7).

For those nine patients with objective responses, steady-state trough plasma concentrations ranged between 63 and 1873 ng/ml (10); interestingly, two patients taking 225 and 300 mg/day had steady-state trough plasma concentrations of gefitinib <100 ng/ml, which suggests that plasma levels <100 ng/ml may result in objective responses in patients with NSCLC.

**Oncology/Pharmacology-like Trials.** Two pharmacology-like Phase I trials determined a dose range for gefitinib given orally on a daily basis and further defined the OBD (8, 9). Secondary objectives were to (a) monitor gefitinib exposure; (b) investigate the feasibility and sensitivity of the Functional Assessment of Cancer Therapy (FACT) questionnaire for lung, head and neck, breast, colorectal, prostate, and ovarian cancer; (c) assess improvements in NSCLC-related symptoms using the seven-item Lung Cancer Subscale of FACT-Lung (11); and (d) select tumor types for Phase II/III studies. Up to 14 patients...
were enrolled at each planned dose level (150–1000 mg/day gefitinib).

A total of 157 patients received 150-1000 mg/day gefitinib (Table 1), with the MTD identified in one trial as 800 mg/day (8) and not reached in the other (9). The most commonly reported AEs (grade 1–2 diarrhea and skin rash) were dose related across the range studied (150–800 mg/day), with dosage interruptions and reductions generally required only at doses >600 mg/day. There was no clear dose-response relationship for disease control, which was observed at all doses (Table 2, with 45 patients receiving gefitinib for ≥3 months, 20 patients receiving gefitinib for ≥6 months, and 7 patients receiving gefitinib for >1 year (1 with a partial response and 6 with stable disease). Patients with NSCLC who had stable disease for ≥6 months also had improvements or stabilization in disease-related symptoms, whereas those patients with disease progression had worse Lung Cancer Subscale (LCS) scores (12). Therefore, duration of treatment and the LCS might be useful in determining clinical activity with gefitinib treatment.

Because the EGFR is present and important for normal skin homeostasis (13, 14), the biological activity of gefitinib was assessed using markers of PD effects from skin biopsies (e.g., levels of phosphorylated EGFR and activated pMAPK; Ref. 15). These biopsies showed that EGFR phosphorylation was abolished and that activated pMAPK levels were significantly reduced in skin biopsies from patients taking gefitinib (Figs. 2A and B, respectively), the lowest dose at which objective tumor responses were noted. These PD analyses indicate that in the skin, gefitinib was exerting maximum biological effect at the lowest dose studied.

DOSE SELECTION FOR PHASE II AND III CLINICAL TRIALS

The gefitinib Phase I trials were designed and planned for the possibility that results might be unclear, because gefitinib was anticipated to be cytostatic rather than induce tumor regression. However, the blinded-review panel was not required because sufficient patients with objective tumor responses and stable disease were observed across a range of tumors to establish a dose-response curve, supported by PD and PK assessments. The dose:response and dose:toxicity relationships observed are shown in Fig. 3; clinical benefit was not dose related at doses ≥150 mg/day, whereas the most common AEs (skin rash and acne) increased with gefitinib dose. These Phase I trial results showed that the OBD for gefitinib is much lower than the MTD, supporting the hypothetical model in Fig. 1B, and they suggested that gefitinib had maximum biological and clinical activity over the dose range 150-1000 mg/day. In addition, PK

Table 1  Patients receiving gefitinib by dose and tumor type in two Phase I pharmacology-like dose-escalation trialsa

<table>
<thead>
<tr>
<th>Gefitinib dose, mg/day</th>
<th>NSCLCb (n = 61)</th>
<th>Ovarian (n = 25)</th>
<th>CRC (n = 28)</th>
<th>HRPC (n = 17)</th>
<th>SCCHN (n = 26)</th>
<th>Total (n = 157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>13</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>225</td>
<td>11</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td>300</td>
<td>13</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>400</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>600</td>
<td>4</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>800</td>
<td>5</td>
<td>2</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>1000</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>17</td>
</tr>
</tbody>
</table>

a References 8 and 9.

b NSCLC, non-small cell lung cancer; CRC, colorectal carcinoma; HRPC, hormone-refractory prostate cancer; SCCHN, squamous cell carcinoma of the head and neck.

Table 2 Patients with disease control who received gefitinib for ≥6 monthsa,b

<table>
<thead>
<tr>
<th>Gefitinib dose, mg/day</th>
<th>No. of patients</th>
<th>Response</th>
<th>Tumor</th>
<th>Time on study, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 (n = 19)</td>
<td>1 PRc</td>
<td>NSCLC</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>225 (n = 7)</td>
<td>1 SD</td>
<td>SCCHN</td>
<td>28+d</td>
<td></td>
</tr>
<tr>
<td>300 (n = 27)</td>
<td>1 SD</td>
<td>Ovarian</td>
<td>9+f</td>
<td></td>
</tr>
<tr>
<td>400 (n = 27)</td>
<td>1 SD</td>
<td>SCCHN</td>
<td>14+h</td>
<td></td>
</tr>
<tr>
<td>600 (n = 20)</td>
<td>1 SD</td>
<td>NSCLC</td>
<td>25+i</td>
<td></td>
</tr>
<tr>
<td>800 (n = 20)</td>
<td>1 SD</td>
<td>NSCLC</td>
<td>14+i</td>
<td></td>
</tr>
<tr>
<td>1000 (n = 17)</td>
<td>1 SD</td>
<td>HRPC</td>
<td>8+j</td>
<td></td>
</tr>
</tbody>
</table>

a ≥ 6 × 28-day treatment periods.
b References 8 and 9.
c PR, partial response; NSCLC, non-small cell lung cancer; SD, stable disease; SCCHN, squamous cell carcinoma of the head and neck; HRPC, hormone-refractory prostate cancer; CRC, colorectal carcinoma.
d Includes time spent on extension compassionate-use trial.
e Patient had a sustained decrease from baseline prostate-specific antigen >50% over 4 months.
f No change in carbohydrate antigen 125 (CA125).
g Patient had a 48% reduction in serum CA125.
h Worsening in prostate-specific antigen levels observed.
studies indicated that plasma levels of gefitinib over this dose range were sufficient for effective EGFR inhibition.

The objective tumor responses observed in patients with NSCLC resulted in two dose levels being selected for Phase II and III NSCLC trials. Although the lowest dose at which objective tumor responses were observed was 150 mg/day, there was potential for individuals receiving this dose to have subtherapeutic exposure as a result of interpatient variability in pharmacokinetics. Accordingly, the slightly higher dose of 250 mg/day was chosen because this dose would ensure adequate gefitinib drug exposure. The second dose chosen was 500 mg/day, which was the highest dose that was well tolerated by most patients on a chronic daily dosing schedule. Both doses were significantly lower than the MTD (approximately one-third and two-thirds of the MTD, respectively), unlike conventional dose selection for chemotherapy agents, which would use the MTD.

PHASE II DOSE-EVALUATION TRIALS IN NSCLC

Two large, dose-randomized, double-blind, parallel-group, multicenter Phase II trials (‘Iressa’ Dose Evaluation in Advanced Lung Cancer 1 and 2) independently evaluated the activity of 250 and 500 mg/day gefitinib in 425 patients with advanced NSCLC (16, 17). These trials allowed a more detailed evaluation of the doses selected from the Phase I trials and included symptom improvement as an additional end point. Both doses were significantly lower than the MTD (approximately one-third and two-thirds of the MTD, respectively), unlike conventional dose selection for chemotherapy agents, which would use the MTD.

REACHING THE TARGET: GEFITINIB TISSUE DISTRIBUTION

Evidence to support the extensive tissue distribution of gefitinib has been provided in PK studies involving healthy volunteers and patients with advanced solid tumors, which found that gefitinib (50–100 mg) had a very high volume of distribution (≥1400 liters; Table 4; Ref. 10). In the Phase I trials, analysis of PD marker levels in the skin also provided evidence that sufficient gefitinib was reaching the skin and inhibiting EGFR signaling (15). Additionally, objective tumor responses observed across a dosage range of 150-1000 mg/day in the Phase I trials indicated that these doses resulted in target inhibition in tumors. These data are supported by preclinical xenograft (LoVo) data showing that, 8 h after the administration of radiolabeled [14C]gefitinib, the tumor:plasma gefitinib ratio was 11:1 (19); radioactivity levels in skin and tumor samples were similar and considerably higher than those in the plasma. Thus, gefitinib targets tumors effectively.

DISCUSSION

Although the primary objective of a Phase I trial is to assess the safety profile of an anticancer agent, some evidence
of antitumor activity is required to justify progression to Phase II trials. For the evaluation of biologically targeted agents, conventional clinical end points should be supplemented with surrogate markers of clinical activity, because these agents might not be expected to cause tumor regression or normal tissue toxicity at maximally effective doses. This review has used the example of gefitinib to show that early clinical trials of biologically targeted agents should aim to identify the OBD using clinical end points and one or more PD parameters. NSCLC objective tumor response data from the Phase I and II trials, in which objective responses were observed across a wide dose range (150–1000 mg/day; Fig. 3), indicate that these doses of gefitinib were sufficient to inhibit EGFR signaling. However, in the absence of an objective response, how do we know that relevant levels of biologically targeted agents are reaching their target tissue? Evidence that gefitinib reaches target tissues and tumors has been supported by the high tumor:plasma ratio observed in xenograft models and by the high volume of distribution of gefitinib (10, 19). Furthermore, PD analyses of biomarker expression have shown that gefitinib at 250 mg/day and 500 mg/day inhibits EGFR-mediated signaling in clinical breast and gastric cancer tumor biopsies (20, 21).

The use of surrogate markers has previously been shown to be feasible in selecting the dose for cetuximab (IMC-C225), a humanized anti-EGFR monoclonal antibody; 200 mg/m² was the lowest dose that saturated the antibody systemic clearance rate and was significantly lower than the MTD (22). In the gefitinib example, when conventional clinical end points were used, doses above a certain threshold did not give better objective tumor responses, whereas AEs were dose-related (Fig. 3). Surrogate markers (including inhibition of EGFR signaling in skin biopsies, duration of treatment, and improvements in disease-related symptoms) were also shown to be feasible for Phase II dose selection. Indeed, the rapid onset of symptom improvement in the Phase II trials along with an observed correlation between symptom improvement and objective tumor response, suggests that symptom improvement may be a rapid surrogate marker of objective tumor response, although additional placebo-controlled studies are needed to clarify this.

Although the gefitinib Phase I trials aimed to explore the OBD in an optimal fashion, there were a number of complications that may also apply in early trials of other novel targeted agents. These included the fact that the patient population was heterogeneous, with a variety of EGFR-expressing tumor types. In addition, there is no certainty that each tumor type will be equally sensitive to gefitinib or that the OBD will be identical in all tumors. Such uncertainties meant that two doses (250 and 500 mg/day) were chosen for Phase II/III trials. Finally, much of the PD data came from skin biopsies rather than tumor biopsies, and, because biopsies are not easy to obtain for many tumor types, this is a significant challenge for any approach relying on tumor PD assessments.

Further refinements in the design of Phase I trials for biologically targeted agents could also be made. One of the complexities of using a blinded-review panel is in the evaluation of TBE based on the relevance of each type of data, because patients will be differently evaluable for specific data of antitumor effects. As such, trials could benefit from cross-validation between experts to obtain a consensus, with focused discussion on discordant cases. If all patients are evaluable for at least one PD parameter (rather than depending on serial biopsies), evidence of TBE could be measured consistently and more

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>IDEAL 1</th>
<th>IDEAL 2</th>
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<tbody>
<tr>
<td></td>
<td>250 mg/day (n = 103)</td>
<td>500 mg/day (n = 106)</td>
</tr>
<tr>
<td>Drug-related grade 3–4 adverse events (%)</td>
<td>8.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30.2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>18.4</td>
<td>19.0</td>
</tr>
<tr>
<td>Disease control rate (%)</td>
<td>54.4</td>
<td>51.4</td>
</tr>
<tr>
<td>Overall survival (mo)</td>
<td>7.6</td>
<td>7.9</td>
</tr>
<tr>
<td>Symptom improvement&lt;sup&gt;d&lt;/sup&gt; (%)</td>
<td>40.3</td>
<td>37.0</td>
</tr>
<tr>
<td>Patients with partial response experiencing symptom improvement (%)</td>
<td>69.2</td>
<td>85.7</td>
</tr>
<tr>
<td>Improved quality of life&lt;sup&gt;e&lt;/sup&gt; (%)</td>
<td>23.9</td>
<td>21.9</td>
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</table>

<sup>a</sup> References 16 and 17.

<sup>b</sup> Reference 28.

<sup>c</sup> Reference 29.

<sup>d</sup> Assessed using the seven-item Lung Cancer Subscale (LCS) of Functional Assessment of Cancer Therapy-Lung (FACT-L).

<sup>e</sup> Assessed using FACT-L.

<sup>f</sup> Reference 30.

### Table 4

<table>
<thead>
<tr>
<th></th>
<th>Healthy volunteers 50–100 mg i.v. (n = 8)</th>
<th>Patients 50 mg i.v. (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of distribution, liter</td>
<td>Mean 1610</td>
<td>Mean 1400</td>
</tr>
<tr>
<td></td>
<td>Range 1230–2540</td>
<td>Range 830–2710</td>
</tr>
<tr>
<td>Plasma clearance&lt;sup&gt;b&lt;/sup&gt; rate, ml/min</td>
<td>Mean 840</td>
<td>Mean 514</td>
</tr>
<tr>
<td></td>
<td>Range 471–1250</td>
<td>Range 194–1460</td>
</tr>
<tr>
<td>Elimination half-life, h</td>
<td>Mean 34</td>
<td>Mean 48</td>
</tr>
<tr>
<td></td>
<td>Range 23–73</td>
<td>Range 10–136</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reference 10.

<sup>b</sup> Geometric mean.
accurately; and, if there were more than one PD parameter per patient, the relative merit of that parameter could be prospectively specified (a weighting factor). Potentially, if evidence of a dose response for TBE is further explored in relation to specific tumors (e.g., by increasing patient numbers across the dose range to focus on the most reliable PD measures), a better dose decision for subsequent trials could be determined.

One major challenge in designing clinical trials for biologically targeted agents and optimizing their use is how to identify a patient population that is likely to benefit from treatment. In the case of some novel targeted agents, such as trastuzumab, high expression of the target itself is used to select the patients to be treated (23, 24). However, the situation with gefitinib is not so straightforward. Although clinical trials have recruited patients with tumor types known to express EGFR, subsequent retrospective gene expression and immunohistochemical analysis of EGFR expression have shown that tumor EGFR expression levels do not correlate with response to gefitinib (25), although it remains possible that phosphorylated EGFR may be more important (26). Thus, sensitivity to gefitinib is likely to be much more complex and dependent on a number of factors, of which the EGFR may be but one (27). Some studies have investigated genes associated with resistance to gefitinib, and one retrospective analysis found that increased expression of gefitinib resistant gene 1 (GRG1) correlated with a decreased probability of responding to gefitinib (25). Such analyses of molecular factors are being explored in a wide-ranging clinical trial program to explore more fully the potential to identify those patients who will benefit from gefitinib treatment.

The clinical trials of gefitinib presented in this review have shown that efficacy and surrogate end points (duration of treatment, improvements in disease-related symptoms, and PD effects) have identified 250 mg/day as the OBD in NSCLC, because higher doses of gefitinib do not give better responses and cause increased toxicity. This recommended dose is one-third of the MTD and results in a favorable benefit-risk ratio.

REFERENCES


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