Salvage Therapy for Advanced Non-Small Cell Lung Cancer: Factors Influencing Treatment Selection

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Key Words. NSCLC • Treatment selection • HER-1/EGFR inhibitors • Second-line • Predictive markers • Erlotinib

Abstract

Novel chemotherapies and molecularly targeted agents have improved outcomes for patients with advanced non-small cell lung cancer (NSCLC). Several efficacious regimens are available, which allows for selection of therapy based on factors such as schedule, toxicity profile, patient-specific needs, and individual preferences of the patient.

Treatment guidelines recommend platinum-based chemotherapy first line for patients with a good performance status. These regimens offer a modest survival advantage over best supportive care. The role of targeted biologic agents in this setting is being assessed in phase II trials. Results to date show promising activity and tolerability.

Erlotinib, docetaxel, and pemetrexed are all approved for patients who progress following one prior regimen for advanced NSCLC. These agents have different tolerability profiles and routes of administration but appear to have similar effects on tumor response and survival, though comparative trials are required to confirm this. Based on the results of a phase III trial, erlotinib is also recommended for third-line use in patients with NSCLC.

Identifying predictive markers of clinical response to therapy may provide an opportunity to better select patient subsets appropriate for specific treatment. Recent data have linked various clinical characteristics and biologic markers with outcome to HER-1/EGFR-targeted agents. However, many of these studies are retrospective and based on small patient numbers, and there is evidence of broad benefit across diverse patient subgroups with erlotinib. Prospective, randomized trials are required to validate potential predictive markers fully before they are applied to clinical practice. The Oncologist 2006;11:655–665

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths in the U.S. However, recent advances in our understanding of the molecular basis of this disease have enabled the development of new, rationally designed, targeted antitumor agents. Most new NSCLC therapies can be broadly classified as targeted “cytotoxic agents” or targeted “biological agents.” Cytotoxic drugs inflict cell death by affecting processes that are commonly overactive or enhanced in tumor compared with normal cells. Biologic agents interact with receptors, ligands, signaling molecules, or genes that are pivotal in tumor growth and development. They may, among other things, inhibit tumor cell proliferation, induce programmed cell death, inhibit angiogenesis, or enhance antitumor immune response [1].

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The U.S. Food and Drug Administration (FDA) recently approved three agents for advanced NSCLC: erlotinib (Tarceva®; Genentech, Inc., South San Francisco, CA, and OSI Pharmaceuticals, Melville, NY), pemetrexed (Alimta®; Eli Lilly and Company, Indianapolis), and gefitinib (Iressa®; AstraZeneca Pharmaceuticals, Wilmington, DE). Many more new agents are being evaluated in clinical trials. Erlotinib and gefitinib are human epidermal growth factor receptor (HER-1/EGFR) tyrosine-kinase inhibitors (TKIs). HER-1/EGFR is commonly dysregulated in NSCLC and between 43% and 83% of NSCLCs overexpress the receptor. It has a pivotal role in tumorigenesis and disease progression [2, 3]. HER-1/EGFR inhibition induces apoptosis, cell-cycle arrest, and tumor growth inhibition [4, 5]. Erlotinib is approved for patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen [6]. Pemetrexed is a multitargeted antifolate compound that disrupts folate-dependent metabolic processes essential for cell replication [7]. It is approved for second-line NSCLC, thus providing a chemotherapeutic alternative to docetaxel (Taxotere®; sanofi-aventis, Bridgewater, NJ). Gefitinib was approved for use after failure of both platinum-based chemotherapy and docetaxel [8]. However, based on negative phase III trial results in NSCLC, the gefitinib product label now restricts its use to patients who are currently benefiting or have previously benefited from the drug [9].

The introduction of new agents, such as HER-1/EGFR TKIs, is a testament to recent advances in basic and translational science, the perseverance of clinicians involved in clinical trials, and, of course, the many patients who participated in the trials. These agents expand and improve the treatments available for patients with NSCLC, although oncologists now have more factors to consider when prescribing therapy, particularly in second-line treatment, where there are several new treatment options. This article addresses the changing landscape of NSCLC therapy, discussing the factors and data that should be considered when selecting the appropriate treatment for these patients.

**Changing Treatment Options for Advanced NSCLC**

**First-Line Treatment**

The goals of therapy for advanced NSCLC are to improve survival and to provide palliation of symptoms. The current clinical practice guidelines from the National Comprehensive Cancer Network® (NCCN) for the first-line treatment of patients with a good performance status (PS) recommend platinum-based chemotherapy, usually in combination with a third-generation cytotoxic compound such as gemcitabine (Gemzar®, Eli Lilly and Company), paclitaxel (Taxol®, Bristol-Myers Squibb, Princeton, NJ), or docetaxel [10]. Clinical trials have yielded comparable results when a platinum is combined with any of the third-generation agents mentioned above [11, 12].

Platinum-based regimens offer a modest survival advantage over best supportive care, but certain agents are commonly associated with nephrotoxicity, neurotoxicity, and myelosuppression [12]. Such toxicities may preclude the use of these regimens in elderly patients or those with a poor PS, although some data suggest elderly patients can benefit from platinum-based chemotherapy doublets [13]. These considerations are important as the median age of newly diagnosed lung cancer patients in developed countries is 68 years, and as many as 40% may be over 70 years old [14]. Furthermore, 30%–40% of patients with advanced NSCLC are estimated to have a poor PS [15]. Concerns over toxicity often deter oncologists from using standard regimens for these patients. For patients deemed at an unacceptable risk from toxicity from combination chemotherapy, single-agent therapy is a reasonable option as it is associated with fewer adverse events [16, 17].

Despite the aggressive use of chemotherapy, the prognosis for patients with advanced, unresectable NSCLC is poor. The median survival in patients with stage IV NSCLC is approximately 8–11 months [18]. More effective, less toxic, first-line treatments are needed and it is hoped that biologic agents used alone or in combination with chemotherapy may fulfill this requirement.

Phase II data suggest that HER-1/EGFR TKIs may be effective as first-line monotherapy, or in combination with chemotherapy for select subsets of patients (i.e., never smokers) [19–26]. However, findings from initial trials of biologic agents combined with chemotherapy were disappointing. Phase III trials of erlotinib and gefitinib with standard first-line chemotherapy failed to improve survival compared with chemotherapy alone and as a result there is currently no role for concurrent chemotherapy and HER-1/EGFR-based therapy in NSCLC [27–30]. However, it has been suggested that HER-1/EGFR-targeted agents may abrogate the effect of chemotherapy when given concurrently. This is supported by preclinical studies that show these targeted agents induce G1 cell cycle arrest, which can reduce the M-phase activity of chemotherapeutic agents such as docetaxel [31, 32]. Consequently, intermittent schedules of erlotinib and docetaxel, designed to achieve pharmacodynamic separation of antitumor activity, were studied in a phase I trial of patients with solid tumors. These combinations did appear to be feasible and active, and a follow-up phase II trial is currently under way in advanced NSCLC (second line) [33].
Recently, the combination of bevacizumab (Avastin®; Genentech, Inc.), an antiangiogenic agent, with chemotherapy has demonstrated a survival advantage as first-line therapy for advanced NSCLC. In a phase III trial conducted by the Eastern Cooperative Oncology Group (E4599), bevacizumab, a vascular endothelial growth factor (VEGF)-targeted antibody, significantly improved overall survival compared with chemotherapy alone when administered in combination with paclitaxel and carboplatin for patients with advanced, nonsquamous NSCLC [34]. These results show that a triplet regimen containing a biologic agent can improve survival in this setting and support further investigation of different regimens.

Second-Line Treatment
Response to first-line therapy is generally short lived, and progression occurs an average of 4–6 months after treatment is discontinued [35]. Many of these patients continue to have a good PS and are candidates for second-line therapy, although not all receive it.

The revised clinical practice guidelines from the NCCN recommend erlotinib, pemetrexed, or docetaxel monotherapy after failure of one prior chemotherapy regimen [10]. The adoption of docetaxel as a standard of care was based on data from two phase III trials [36, 37]. In the first trial, docetaxel (75 mg/m² every 3 weeks) significantly prolonged median and 1-year survival duration compared with best supportive care (median survival, 7.5 months vs. 4.6 months; \( p = .010 \); 1-year survival, 37% vs. 12%), although the response rate was low (5.5%) [37]. In the second study, the 6-month and median survival rates were similar for docetaxel and vinorelbine (Navelbine®; GlaxoSmithKline, Philadelphia) or ifosfamide (Mitoxana®, Baxter Oncology, Deerfield, IL) [36]. However, the 1-year survival rate was significantly greater with docetaxel (75 mg/m²) than vinorelbine or ifosfamide (32% vs. 19%; \( p = .025 \)). There was a significant improvement in various quality-of-life parameters in both studies for patients receiving docetaxel [36, 37].

In August 2004, the FDA approved pemetrexed for second-line NSCLC based on data from a randomized, phase III trial [38]. In that trial, median survival with pemetrexed (500 mg/m² every 3 weeks) was 8.3 months versus 7.9 months with docetaxel (75 mg/m² every 3 weeks; not significantly different). Response rates and times to disease progression for both agents were comparable. The incidence of side effects (grade 3 or 4 neutropenia, febrile neutropenia, and neutropenia with infections) with pemetrexed was significantly lower than with docetaxel (\( p \leq .004 \)), and hospitalizations for neutropenic fever (\( p < .001 \)) and other drug-related adverse events (\( p = .092 \)) were also lower with pemetrexed. Patients randomized to the pemetrexed arm received supplementation with vitamin B₁₂ and folic acid [7].

Erlotinib, an oral HER-1/EGFR TKI, was approved by the FDA in November 2004 and by the European Commission in September 2005 for patients with advanced or metastatic NSCLC who have failed at least one prior chemotherapy regimen. Erlotinib is the first and only HER-1/EGFR inhibitor to show a survival benefit in NSCLC in a randomized, placebo-controlled setting. In the pivotal phase III trial (BR.21), median survival on erlotinib (150 mg/day) was 6.7 months compared with 4.7 months on placebo (a relative improvement of 42.5%; \( p < .001 \)) [40]. After 1 year, 29.7% of patients were alive in the erlotinib group compared with 20.5% in the placebo group. Moreover, progression-free survival and tumor response were significantly better with erlotinib. An exploratory univariate analysis demonstrated that the beneficial effect of erlotinib on survival was similar across most patient subgroups. Patients who had received one or two prior chemotherapy regimens responded equally well to erlotinib (Fig. 1). In addition, treatment with erlotinib gave a significant and clinically meaningful benefit in delaying the time to deterioration of cough, dyspnea, and pain versus placebo [39, 40]. In line with other HER-1/EGFR inhibitors, rash and diarrhea were the most common adverse events [39].

The effectiveness of erlotinib highlights the potential of biologic agents in NSCLC, and a number of other agents are currently under evaluation in the second-line setting. They include cetuximab (Erbitux®; ImClone Systems, Inc., New York), a HER-1/EGFR-targeted monoclonal antibody; bortezomib (Velcade®, Millennium Pharmaceuticals, Inc., Cambridge, MA), a proteasome inhibitor; ZD6474 (AstraZeneca Pharmaceuticals), a VEGFR-2 TKI; and talabostat (Point Therapeutics, Inc., Boston, MA), an inhibitor of dipeptidyl peptidases such as fibroblast activation protein (FAP) [41–44].

Another cytotoxic agent that has been evaluated as a second-line therapy for NSCLC is gemcitabine. A number of phase II monotherapy trials have been undertaken, and response rates of 0%–21% have been noted [45]. However, the efficacy of gemcitabine has not been tested in phase III trials for second-line therapy. Combination regimens have also been evaluated in this setting, though there is no evidence of additional benefit over monotherapy. The combination of gemcitabine and docetaxel demonstrated a higher response rate (30%–33%), longer median time to progression (5.5–6 months), and longer median survival (7.3–8 months) [46, 47]. However, this has not been studied in phase III trials. Activity has also been observed in combination with etoposide, topotecan, and vinorelbine with response rates of 21%, 15%, and 6%–21%, respectively [45].
Third-Line Treatment

Erlotinib is the only agent currently recommended without restrictions for third-line use in patients with NSCLC [6, 10]. The approval of erlotinib third line was based on the response and survival data from the BR.21 trial, in which 50% of patients received erlotinib monotherapy after failure of two or more chemotherapy regimens [6, 39].

In May 2003, gefitinib was approved by the FDA for advanced or metastatic NSCLC following failure of both platinum-based and docetaxel chemotherapies. Approval was based on response data from a double-blind, randomized, phase II trial [48]. The objective tumor response rate with gefitinib (250 mg/day) was 13.6% [8, 48], and symptoms improved in 43% of patients [48]. As a condition of approval, the FDA mandated a phase III placebo-controlled trial (Iressa Survival Evaluation in Lung Cancer [ISEL]) to establish a survival advantage with gefitinib. Data from the ISEL trial \( (n = 1,692) \) showed that gefitinib did not significantly prolong survival compared with placebo (median, 5.6 months vs. 5.1 months; hazard ratio, 0.89; \( p = .87 \)) [52]. Consequently, the FDA made changes to the product label, limiting gefitinib use to patients currently or previously benefiting from this agent, and restricting new access to patients enrolled in a clinical study conducted under an investigational new drug application [9]. Given this direction from the FDA, erlotinib should be considered for third-line therapy if it has not been used second line.

Considerations When Choosing Treatment for Patients who Have Progressed After First-Line Chemotherapy

The development of new therapies and combination strategies for advanced NSCLC means there are several options for first-, second-, and third-line treatment (Fig. 2). The
first-line therapy of choice is combination chemotherapy, preferably a platinum-containing regimen, provided the patient is suitable for such aggressive therapy. Upon progression, therapy with docetaxel, pemetrexed, or erlotinib is considered optimal. When choosing second-line therapy, factors to be considered include efficacy, tolerability profile, and patient preference.

**Efficacy**

Response rate and survival data for docetaxel, pemetrexed, and erlotinib are summarized in Table 1 [6, 37, 38]. Docetaxel and erlotinib both prolong survival compared with best supportive care and, based on the comparative trial, pemetrexed has efficacy comparable with that of docetaxel. Erlotinib has not been compared directly with either docetaxel or pemetrexed, though the efficacy results reported in the pivotal trials for all these agents appear to be similar. Although the median survival time of 6.7 months for erlotinib in the BR.21 trial is shorter than that reported for docetaxel or pemetrexed, it is confounded by the inclusion of patients with poor PS scores (2 or 3) on the Eastern Cooperative Oncology Group [ECOG] scale) and those who received two prior regimens [38, 39]. In BR.21 25% of patients on the erlotinib arm had PS score of 2 and 9% had PS score of 3. In comparison, patients with a PS score of 3 were excluded from the phase III trials of docetaxel and pemetrexed and the proportion of patients with a PS score of 2 ranged from 11%–24%. For patients with a good PS score (0 or 1) who received erlotinib second line in BR.21, the median survival time was 9.4 months, which is comparable with the 9.1 months observed with docetaxel and 9.4 months with pemetrexed in similar patient subsets (Table 1). The lack of efficacy data with docetaxel and pemetrexed in patients with a PS score of 3 makes erlotinib a preferred second-line therapy option in this group.

Interestingly, the survival advantage with second-line therapy of advanced NSCLC occurs despite a low response rate (<10%). This suggests that the clinical benefit derived from salvage therapy is achieved primarily through disease stabilization.

Clinical trials are currently under way to compare the efficacy of erlotinib with that of single-agent chemotherapy for salvage therapy of advanced NSCLC. Although erlotinib has shown significant survival benefit across most patient subtypes, there are some subtypes that appear to exhibit greater benefit (such as never smokers or those with bronchioloalveolar histology), and this is also being investigated further in clinical studies. Response to prior chemotherapy is another factor that may determine the choice of optimal second-line therapy. For instance, will second-line chemotherapy be equally efficacious in a patient experiencing rapid disease progression as in a responder to first-line therapy? Prior treatment with paclitaxel does not appear to reduce the second-line efficacy of either docetaxel or pemetrexed [36, 38], but for patients who do progress rapidly following first-line chemotherapy, would a mechanistically distinct chemotherapeutic agent or a targeted biologic agent be a better second-line choice? The answers to these questions are unclear at this time, and warrant further clinical evaluation.
In the absence of any obvious differences in efficacy, tolerability is another important consideration. Docetaxel, pemetrexed, and erlotinib all have distinct toxicity profiles (Table 2) [6, 7, 53], and their differences influence the choice of second-line therapy. The principal toxicities associated with docetaxel are myelosuppression, fatigue, alopecia, and peripheral edema. Though myelosuppression, skin rash, and diarrhea are also associated with pemetrexed, in the phase III study by Hanna et al. [38], there were fewer hospitalizations and episodes of febrile neutropenia than with docetaxel. Both docetaxel and pemetrexed require the use of concomitant corticosteroids to ameliorate toxicity, in particular, nausea, vomiting, and rash. Vitamin supplementation with both folic acid and vitamin B12 is also mandatory with pemetrexed. Erlotinib is not commonly linked to hematologic toxicities and does not require any premedication, but can cause skin rash and diarrhea, which are usually mild to moderate and generally manageable [6].

Several clinical trials have explored alternative dosing schedules in an attempt to lower the toxicity profile of docetaxel. The standard regime of 75 mg/m² every 3 weeks has been compared with 33–40 mg/mm² weekly doses of docetaxel [51–54]. These studies suggest that the weekly schedules are often associated with lower grade 3 or 4 adverse events, particularly neutropenia and febrile neutropenia, and have a similar efficacy profile to the 3-week schedule (although there is a trend toward better disease control with the 3-week schedule) [55]. This suggests that the weekly docetaxel regimens may offer viable alternatives to 3-weekly docetaxel in patients at risk of severe neutropenia.

Another factor to consider in treatment selection is the toxicity profile experienced by the patient during first-line chemotherapy. A biologic agent with nonoverlapping toxicity may be particularly appropriate for those experiencing severe residual chemotherapy-related side effects.

### Third-Line Treatment Options
The majority of patients who receive second-line therapy will not be candidates for third-line treatment because of a decline in PS or the development of symptoms that warrant local therapy. Therefore, it would appear reasonable to consider all available options (based on efficacy, tolerability,

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**Table 1. Efficacy data for docetaxel, pemetrexed, and erlotinib [6, 7, 37, 38, 53]**

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel (75 mg/m²) vs. best supportive care</th>
<th>Docetaxel (75 mg/m²) vs. pemetrexed</th>
<th>Erlotinib vs. best supportive care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 55)</td>
<td>(n = 288)</td>
<td>(n = 488)</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>5.5</td>
<td>9.1</td>
<td>8.9</td>
</tr>
<tr>
<td>Median survival (mos)</td>
<td>7.5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>7.9</td>
<td>6.7</td>
</tr>
<tr>
<td>1-year survival (%)</td>
<td>37</td>
<td>29.7</td>
<td>31.2</td>
</tr>
<tr>
<td>Median survival (mos) for PS 0/1, second-line patients</td>
<td>7.9</td>
<td>9.1</td>
<td>9.4</td>
</tr>
</tbody>
</table>

<sup>a</sup>Patients with a PS score ≤2 and who had received one or two prior chemotherapy regimens were eligible for inclusion.

<sup>b</sup>Patients with a PS score ≤2 and who had received one prior chemotherapy regimen were eligible for inclusion.

<sup>c</sup>Patients with a PS score ≤3 and who had received one or two prior chemotherapy regimens were eligible for inclusion.

<sup>d</sup><i>p</i> = .010; <sup>e</sup><i>p</i> < .001.

**Table 2. Toxicity profile of second-line therapy agents [6, 7, 53]**

<table>
<thead>
<tr>
<th></th>
<th>Incidence (%)</th>
<th>Docetaxel 75 mg/m² (n = 176)</th>
<th>Pemetrexed (n = 265)</th>
<th>Erlotinib&lt;sup&gt;a&lt;/sup&gt; (n = 485)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td>84</td>
<td>11</td>
<td>Not listed</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>All grades</td>
<td>84</td>
<td>11</td>
<td>Not listed</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>65</td>
<td>5</td>
<td>Not listed</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>All grades</td>
<td>84</td>
<td>13</td>
<td>Not listed</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>49</td>
<td>5</td>
<td>Not listed</td>
</tr>
<tr>
<td>Anemia</td>
<td>All grades</td>
<td>91</td>
<td>33</td>
<td>Not listed</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td>23</td>
<td>21</td>
<td>52</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>8</td>
<td>&lt;1</td>
<td>7</td>
</tr>
<tr>
<td>Skin/rash</td>
<td>All grades</td>
<td>20</td>
<td>17</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>&lt;1</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>41&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td>41&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>As monotherapy for unresectable, locally advanced or metastatic non-small cell lung cancer previously treated with platinum-based chemotherapy.

<sup>b</sup>Categorized as pulmonary adverse events.
and other factors such as convenience) in the second-line setting, as opposed to saving therapies for later use following disease progression. Erlotinib is the only agent that is currently approved third line for advanced NSCLC. However, it may not always be rational to save erlotinib for third-line use, given its demonstrated survival and tolerability benefits second line. In addition, using erlotinib second line does not preclude the subsequent use of chemotherapeutic agents, though the efficacy of chemotherapy in the third-line setting is an area that needs to be studied carefully. Will chemotherapy benefit patients who received a prior HER-1/EGFR TKI, or will the use of erlotinib after platinum-based chemotherapy be better tolerated than another chemotherapy regimen? Until answers to these questions are available, one cannot make treatment selections for second-line therapy based on the anticipated need for third-line intervention.

Mode of Administration and Patient Preference

Both patient convenience and the likelihood of patient compliance should be considered when selecting second-line therapy. The dosing regimens of docetaxel, pemetrexed, and erlotinib are summarized in Table 3. Erlotinib is administered by the oral route on a daily basis, while standard regimens of docetaxel and pemetrexed are administered via i.v. infusion every 3 weeks. Pemetrexed is administered over 10 minutes and docetaxel over 60 minutes. Given the comparable efficacy and tolerability of these agents, it is important to discuss treatment options with the patient. Where appropriate, providing patients with background information on the efficacy, adverse events, and routes of administration may allow them to make an informed decision.

Predictive Markers of Sensitivity to HER-1/EGFR TKIs

Identifying predictive markers of clinical response to therapy may provide an opportunity to better select patient subsets appropriate for specific treatment. Results from the BR.21 trial demonstrated that erlotinib had a beneficial effect on survival across the whole study population [6]; however, emerging data suggest possible links between certain patient characteristics and better outcome to treatment with the HER-1/EGFR TKIs erlotinib and gefitinib for NSCLC. These characteristics include patients with no prior or current smoking (having smoked fewer than 100 cigarettes in a lifetime), female gender, having adenocarcinoma and/or bronchioalveolar histology, and Asian ethnicity [33, 56–58]. The reasons behind the higher efficacy of HER-1/EGFR TKIs are not entirely clear, though the higher prevalence of HER-1/EGFR mutations in these subsets could be a possible explanation.

A relationship between HER-1/EGFR overexpression and response to HER-1/EGFR-targeted agents remains to be firmly established, as results have been contradictory. In the BR.21 trial, there was a correlation between high HER-1/EGFR protein expression and higher response rate, but not survival [59]. The link between HER-1/EGFR expression and response was absent in the TALENT or TRIBUTE studies, in which erlotinib was combined with chemotherapy [60, 61], and in two phase II trials of single-agent gefitinib in advanced, refractory NSCLC (Iressa Dose Evaluation in Advanced Lung Cancer [IDEAL]1 and IDEAL2) [62]. It is notable that, in colorectal cancer, data relating to HER-1/EGFR expression and response to the HER-1/EGFR-targeted monoclonal antibody cetuximab are also contradictory, with some trials reporting a positive correlation and others observing no relationship [63, 64].

Amplification of the HER-1/EGFR gene has recently been linked to a higher likelihood of response and extended survival with HER-1/EGFR TKIs. Data from the BR.21 and Southwest Oncology Group (SWOG) 0126 studies have shown a longer median survival duration for patients whose tumors had either gene amplification or high gene copy numbers [40, 65]. A relationship between HER-1/EGFR gene copy number and response to cetuximab has also been observed in patients with colorectal cancer [64].

Table 3. Dosing regimens for docetaxel, pemetrexed, and erlotinib [6, 7, 53]

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel</th>
<th>Pemetrexed</th>
<th>Erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>Every 3 weeks</td>
<td>Every 3 weeks</td>
<td>Daily</td>
</tr>
<tr>
<td>Route and duration of administration</td>
<td>i.v. over 1 hour</td>
<td>i.v. over 10 minutes</td>
<td>Orally at least 1 hour before or 2 hours after food</td>
</tr>
<tr>
<td>Pre- and concomitant medication regimens</td>
<td>Oral corticosteroid for 3 days starting 1 day prior to docetaxel administration</td>
<td>Oral dexamethasone for 3 days starting 1 day prior to pemetrexed administration; daily folic acid from 7 days prior through to 21 days after pemetrexed administration; intramuscular vitamin B12 in the week preceding the first dose of pemetrexed and every three cycles thereafter</td>
<td>None</td>
</tr>
</tbody>
</table>
However, these observations have yet to be confirmed in prospective trials and should not form the basis of decision making in routine care. Studies have also explored possible correlations between expression of HER-1/EGFR downstream signaling components, phosphorylated mitogen-activated protein kinase (pMAPK) and phosphorylated protein kinase B (pAkt), but the results are also contradictory [60, 66–69].

Recent findings suggest that potentially predictive patient characteristics may be indicative of somatic mutations in the HER-1/EGFR TK domain. The mutations generally occur on exons 19 and 21 and are usually amino acid deletions or substitutions [70–72]. They appear more common in adenocarcinomas, tumors from never smokers, and women [71–74]. Their incidence also appears higher in Japanese and Asian patients than in whites [71, 75]. It has also been suggested that acquired resistance to erlotinib and gefitinib is associated with a second mutation in the HER-1/EGFR TK domain at position 790 [76, 77].

Retrospective analysis of clinical data shows that many patients who respond to treatment with erlotinib and gefitinib have HER-1/EGFR mutations [60, 65, 70–72, 78, 79]. Most studies examined the relationship between mutation and response to therapy. However, prolonged survival is arguably the more important outcome with these agents and assessing the relationship between any predictive marker and survival is essential. Recent data with gefitinib in patients with NSCLC recurring after surgery show survival was significantly longer in patients with mutations; gefitinib was effective in 83% of patients with mutations compared with 10% of patients without them. However, tumor progression was also observed in a small minority of patients harboring mutations [74]. Another study with gefitinib in NSCLC demonstrated partial response rates of 64.7% in patients with HER-1/EGFR mutations compared with 13.7% in patients without mutations, and patients with HER-1/EGFR mutations (including responders and nonresponders) had a significantly longer time to progression (21.7 vs. 1.8 months) and overall survival time (30.5 vs. 6.6 months) [80].

In contrast, there was no evidence that patients with mutations gained greater benefit from erlotinib than those with wild type in BR.21 in terms of response or overall survival [59]. The validity of the BR.21 data is supported by the observation that patients who had tumor tissue samples analyzed for mutation status were similar to the overall trial population (e.g., in terms of disease severity, PS, or prior treatment regimens) [59]. Interestingly, preclinical data for cetuximab also suggest that HER-1/EGFR mutations do not sensitize NSCLC cell lines to treatment [81].

Considered together, current data indicate the potential for patient selection based on both clinical and molecular determinants of targeted therapy. They suggest certain patient subsets may be extremely sensitive to HER-1/EGFR-targeted agents, and could potentially benefit from these as frontline therapy. Studies are already under way to evaluate the efficacy of erlotinib first line in enriched patient subsets. However, available data on predictive markers are retrospective and based on small numbers of patients, and should therefore be interpreted with caution. The variable results observed, and differing conclusions drawn by experts in labs and cooperative groups from around the world, underscore the challenges of applying such predictive marker data in clinical practice, and the need for further research.

It is hoped that useful information on the prognostic value of HER-1/EGFR status will be obtained from two postmarketing studies of erlotinib in NSCLC. In the SATURN (erlotinib vs. placebo maintenance therapy) and TITAN (erlotinib vs. pemetrexed or docetaxel second-line) trials, HER-1/EGFR status is to be determined prior to randomization. However, at the present time, there is insufficient evidence to guide clinical practice.

**Summary**

These are exciting times for oncologists who treat patients with NSCLC, as several new agents have recently become available. While these developments are encouraging, it places the onus on the treating physician to carefully consider all available options and choose the regimen that has the best likelihood of benefiting the individual patient. Increasingly, with therapeutically equivalent options, convenience and patient preference are important issues to consider. The value of certain clinical characteristics (such as never-smokers, female gender, documented presence of HER-1/EGFR mutations, and adenocarcinoma or bronchioloalveolar histology) in predicting benefit from erlotinib remains to be proven. Current data are inconclusive, and prospective trials are required to clarify the use of these characteristics in selecting patients for therapy.

An efficacy plateau may have been reached with existing second-line chemotherapies in advanced NSCLC, and novel combinations and agents are urgently needed to improve outcomes for patients who progress following prior chemotherapy. Effective strategies to optimize newer targeted agents such as erlotinib will hopefully be defined by ongoing studies. Combining agents that target different oncogenic pathways or multiple steps of the same cascade is a promising strategy although, at present, such combinations should only be used in the clinical trial setting. It is our hope that trial results will shed more light on patient selection strategies to use novel agents in an optimal manner in the treatment of NSCLC.
DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

Alan B. Sandler has acted as a consultant for Genetech, OSI, and Eli Lilly and has received research support from Genetech. Suresh Ramalingam has acted as a consultant for Genetech and Eli Lilly.

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