Salvage Therapy in Patients with Advanced Non-small Cell Lung Cancer

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Patients with advanced non-small cell lung cancer continue to have a poor prognosis; most die from the disease within 1 year. Chemotherapy is beneficial for some patients in the first-line metastatic setting. Three agents, namely docetaxel, pemetrexed, and erlotinib, are approved by the United States Food and Drug Administration as treatment in the second-line setting. In this article, we examine the data supporting the use of these agents in the second-line setting and review data from other completed trials. Lastly, we propose strategies to advance the treatment of patients with non-small cell lung cancer.

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Lung cancer represents a significant cause of morbidity and mortality in the United States and worldwide. Advances in the treatment of patients with non-metastatic lung cancer have been realized in the last few years, which will result in fewer patients who will die from this disease. The greatest reduction in the burden of lung cancer will be realized when decreased tobacco consumption becomes commonplace throughout the world. Until such time, we will continue to care for hundreds of thousands of patients with metastatic NSCLC each year.

Modest gains in survival time and improvements in overall quality of life (QoL) are associated with the use of chemotherapy in the first-line metastatic setting, primarily for patients with an ECOG performance status (PS) of 0 or 1. Routine use of 5HT3 antagonists and other improvements in supportive care have allowed most patients to tolerate chemotherapy, and most are treated for four to six cycles with first-line therapy. Unfortunately, disease progression after first-line therapy is universal in this patient population, usually within 3 to 5 months of first-line chemotherapy. Survival times remain poor, with most patients dying within 1 year. The effects of cancer on the individual are devastating: weight loss, diminished appetite, profound fatigue, breathlessness, pain, and wasting are common. Ongoing efforts to find improved therapies remain a great challenge. Recently conducted randomized trials have demonstrated the benefits of second- and even third-line therapy. In this article, we examine the data supporting the use of these agents in the second-line setting and review data from other completed trials. We propose strategies to advance the treatment of patients with NSCLC.

Docetaxel

Before 2000, evidence that use of second-line chemotherapy for patients with advanced NSCLC resulted in a survival benefit over best supportive care (BSC) alone was lacking, and no drugs were approved for use by the United States Food and Drug Administration (FDA). In a landmark study, Shepherd et al. reported that treatment with docetaxel 75 mg/m² IV once every 3 weeks could improve survival versus BSC among patients with recurrent NSCLC previously treated with chemotherapy. Initially, patients in the docetaxel arm received 100 mg/m²; after several patients died from drug-related adverse events, docetaxel was modified to 75 mg/m². Overall, 49 patients were treated with 100 mg/m², 55 patients received 75 mg/m², and 100 patients were in the BSC arm. Patients enrolled in this trial had not received a taxane in first-line treatment; 75% had a performance status (PS) of 0/1, and 75% were being treated in the second-line setting, whereas others had received two prior regimens. Although the response rate was modest (7.1%) in the docetaxel arm, more than 50% of patients had confirmed non-progressive disease as their best response (Table 1). The median survival time (MST) and 1-year survival rates were prolonged in the docetaxel arm compared with BSC alone, which confirms that patients with stable disease may also realize survival benefits. As patients are treated with palliative intent, it is especially important in the second-line setting that treatment does not cause toxicity that outweighs the modest survival gains. Indeed, treatment with docetaxel improved the overall QoL in the treated group as a whole.

Confirmation of the benefits of docetaxel in the second-line setting were realized at approximately the same time when a multi-institutional randomized trial by Fossella et al. was reported. In this trial, patients previously treated with chemotherapy were randomized to either docetaxel 75 mg/m² or 100 mg/m² once every 3 weeks versus a control arm consisting of either vinorelbine or ifosfamide. In contrast to the study by Shepherd et al., patients in this study were allowed treatment with a prior taxane (42% of patients). Treatment with the higher dose of docetaxel did not confer additional benefits versus the 75 mg/m² dose but simply...
resulted in more toxicity to the patients. The activity of docetaxel was confirmed to be modest (<10%) but was numerically higher than the control arm (<1%). One-year survival was prolonged for the docetaxel 75 mg/m² arm. Interestingly, the use of paclitaxel in the first-line setting was not predictive of response to docetaxel on this study.

The United States FDA granted full approval for docetaxel 75 mg/m² IV once every 3 weeks in the second-line setting in 1999 based on these randomized studies. The introduction of second-line treatment fulfilled an unmet need in lung cancer treatment. As with many agents, the use of FDA-approved drugs may prove to have more side effects and less effectiveness when used in a general patient population, compared with a study group. Many patients treated off-study may not be eligible for treatment in clinical trials because of co-morbidities, poor PS, or other reasons. As the use of docetaxel became widespread in the United States, it became apparent that treatment with the approved dose and schedule was intolerable for many patients, particularly because of neutropenic complications. In the study populations of Fosella et al. and Shepherd et al., 54% had grade 4 neutropenia, and 67% had grade 3 or 4 neutropenia, respectively (Table 2). The label for docetaxel lists an approximate rate of 8.9% and a MST of approximately 6 months.18 Results of a phase III randomized trial comparing pemetrexed with docetaxel in the second-line setting have been reported.19 In this study, 571 patients received either pemetrexed 500 mg/m² IV on day 1 with vitamin B₁₂, folic acid, and dexamethasone or docetaxel 75 mg/m² IV with dexamethasone every 21 days. Of these patients, 88% had a PS of 0 or 1, 35% had an objective response to first-line therapy, 50% had received first-line chemotherapy within 3 months of entering

given on a weekly basis were explored in phase II trials. Additional improvements in efficacy were also hoped to be realized as lower dose taxanes are thought to exert an additional anti-angiogenic effect. Initial phase II trials of weekly docetaxel seemed to support its widespread use.10–12

Three randomized phase III trials comparing the every 3 weeks and weekly regimens of docetaxel have failed to confirm improvements in efficacy.13–15 Docetaxel was given at doses of 33 to 36 mg/m² weekly for 6 of 8 weeks or 3 of 4 weeks. Response rates for weekly docetaxel are approximately 6%, median survival times are 5 to 6 months, and 1-year survival rates are 20% to 30%. The every 3 weeks schedule was associated with increased incidence of neutropenia, infection, and alopecia, and the weekly schedule with higher rates of nail changes, diarrhea, mucositis, and anemia. The studies by Schuette et al. and Gridelli et al. also explored Qol issues and failed to demonstrate significant differences. When clinicians are faced with the decision on treatment in the second-line setting, convenience to patients is of paramount importance, because survival gains are modest and life expectancy is short. The randomized data fail to justify the use of the more inconvenient weekly regimen of docetaxel for most patients. A weekly regimen should be considered if neutropenia is a primary concern.

**Pemetrexed**

Pemetrexed has demonstrated single-agent activity in NSCLC, with a RR of 17% to 23% in phase II studies of previously untreated patients.16,17 A phase II study of pemetrexed in patients with advanced NSCLC who had disease progression during or within 3 months of completing first-line chemotherapy (chemorefractory) demonstrated a response rate of 8.9% and a MST of approximately 6 months.18 Results of a phase III randomized trial comparing pemetrexed with docetaxel in the second-line setting have been reported.19 In this study, 571 patients received either pemetrexed 500 mg/m² IV on day 1 with vitamin B₁₂, folic acid, and dexamethasone or docetaxel 75 mg/m² IV with dexamethasone every 21 days. Of these patients, 88% had a PS of 0 or 1, 35% had an objective response to first-line therapy, 50% had received first-line chemotherapy within 3 months of entering

### TABLE 1. Efficacy with Docetaxel 75 mg/m² every 3 weeks in Phase III studies

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>RR</th>
<th>SD</th>
<th>TTP</th>
<th>Median survival</th>
<th>1-year survival</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanna et al.19</td>
<td>288</td>
<td>8.8%</td>
<td>46.4%</td>
<td>2.9 months</td>
<td>7.9 months</td>
<td>29.7%</td>
</tr>
<tr>
<td>Fossella et al.9</td>
<td>120</td>
<td>6.7%</td>
<td>36%</td>
<td>8.5 weeks</td>
<td>5.7 months</td>
<td>32%</td>
</tr>
<tr>
<td>Shepherd et al.7</td>
<td>55</td>
<td>7.1%</td>
<td>47.3%</td>
<td>10.6 weeks</td>
<td>7.5 months</td>
<td>37%</td>
</tr>
<tr>
<td>Camps et al.13</td>
<td>131</td>
<td>9.3%</td>
<td>34.1%</td>
<td>2.7 months</td>
<td>6.6 months</td>
<td>27%</td>
</tr>
<tr>
<td>Schuette et al.14</td>
<td>103</td>
<td>12.6%</td>
<td>37.9%</td>
<td>3.4 months</td>
<td>6.3 months</td>
<td>26.9%</td>
</tr>
<tr>
<td>Gridelli et al.15</td>
<td>110</td>
<td>2.7%</td>
<td>NR</td>
<td>NR</td>
<td>21 weeks</td>
<td>21%</td>
</tr>
</tbody>
</table>

**RR, response rate; SD, stable disease; TTP, time to progression; OS, overall survival; NR, not reported.**

### TABLE 2. Grade 3/4 toxicities of weekly and every 3 weeks docetaxel, pemetrexed, and erlotinib

<table>
<thead>
<tr>
<th>Patients</th>
<th>Docetaxel 75 mg/m² (3W)</th>
<th>Docetaxel 75 mg/m² (3W)</th>
<th>Docetaxel36 mg/m² (1W)</th>
<th>Pemetrexed 500 mg/m²</th>
<th>Erlotinib 150 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>67.3%</td>
<td>54%</td>
<td>3.2%</td>
<td>5.3%</td>
<td>NR</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1.8%</td>
<td>8%</td>
<td>0.8%</td>
<td>1.9%</td>
<td>NR</td>
</tr>
<tr>
<td>Infection</td>
<td>5.5%</td>
<td>0</td>
<td>NR</td>
<td>0</td>
<td>2%</td>
</tr>
<tr>
<td>Anemia</td>
<td>5.5%</td>
<td>0</td>
<td>4.8%</td>
<td>4.2%</td>
<td>NR</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>2%</td>
<td>0.8%</td>
<td>2%</td>
<td>NR</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.6%</td>
<td>3%</td>
<td>3.2%</td>
<td>2.6%</td>
<td>3%</td>
</tr>
<tr>
<td>Rash</td>
<td>NR</td>
<td>NR</td>
<td>1.6%</td>
<td>0.8%</td>
<td>9%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.8%</td>
<td>2%</td>
<td>3.2%</td>
<td>0.4%</td>
<td>6%</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1.8%</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Neurosensory</td>
<td>1.8%</td>
<td>1%</td>
<td>3.2%</td>
<td>0</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR, not reported; 3W, every 3 weeks; 1W, every week.
this trial, and only 25% of patients had received a prior taxane. The RR for each agent was approximately 9%, and an additional 45% of patients had stable disease. All efficacy parameters were comparable between both agents (table 1), but there were significant differences in the toxicity profiles (table 2). Significantly more patients in the docetaxel arm experienced grade 3/4 neutropenia (40.2% versus 5.35%; \( p < 0.001 \)), neutropenic fever (12.7% versus 1.9%; \( p < 0.001 \)), and infection with neutropenia (3.3% versus 0%; \( p < 0.004 \)). More patients in the docetaxel arm required hospitalization and the use of growth factor support. Grade 3/4 non-hematologic toxicities were similar in the two arms except for a higher rate of alopecia in the docetaxel arm and higher rates of ALT elevation in the pemetrexed arm. When considering all grades of toxicity, more patients in the docetaxel arm also experienced higher rates of diarrhea and neurosensory toxicities. Both agents result in very low rates of grade 3/4 nausea, but a substantial number of patients do experience grade 1 or 2 nausea. Because grade 1/2 nausea is unpleasant for the patients, one must consider the use of prophylactic 5HT3 antagonists for both agents.

**Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors**

The epidermal growth factor receptor (EGFR) has proven to be an important target in some patients with NSCLC. Although the EGFR is overexpressed in most cases of NSCLC, inhibition of this target results in responses in only 10% to 20% of patients. Two orally active tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib, have been approved by the United States FDA for the treatment of relapsed NSCLC. Despite no phase III data, gefitinib was licensed by the United States FDA as monotherapy filling an unmet need at the time for third-line therapy in NSCLC. Approval was based on two phase II studies (IDEAL-1 and 2) randomizing patients to two different doses of gefitinib, which demonstrated a RR of approximately 10% with improvements in symptoms in 40% of patients. Response to gefitinib seemed independent of whether it was given as second- or third-line treatment (as was done in IDEAL-1) or beyond third-line treatment (as in IDEAL-2). Gefitinib seemed more active in Japanese patients, women, never smokers, and those with adenocarcinoma. Although accelerated approval was granted for gefitinib, confirmatory studies were still required by the FDA to meet the requirements of full licensing approval.

The Iressa Survival Evaluation in Lung Cancer (ISEL) was a randomized, double-blind, placebo-controlled phase III trial conducted in 28 countries. In this study, 1692 patients with advanced NSCLC who had received at least one previous chemotherapy regimen were randomized in a 2 to 1 ratio to gefitinib 250 mg once daily or placebo. The overall response rate was significantly higher in the gefitinib group (8% versus 1.3%; \( p = 0.0001 \)). In the exploratory subgroup analysis, the largest difference in response was seen among never smokers, women, patients with adenocarcinoma, and patients of Asian origin, as expected from the results of the two phase II trials. The most common adverse events were similar to those observed in IDEAL-1 and IDEAL-2, predominantly diarrhea and rash, mostly grade 1/2. The incidence of pneumonitis was equal in both arms (1%). Disappointingly, there was no statistically significant difference in median survival between the two groups (Table 3). Based on this study, gefitinib has been now pulled from the United States market, except for patients who continue to have a response to the drug.

Erlotinib is also a potent, reversible, orally active EGFR-TKI. Shepherd et al. randomized 731 patients with stage IIIB or IV NSCLC, with PS 0-3, who had received one or two prior chemotherapy regimens in a 2 to1 ratio to erlotinib 150 mg daily or placebo. The response rate was 8.9% for erlotinib and less than 1% in the placebo arm (\( p < 0.001 \)). In contrast to chemotherapy, response to erlotinib was independent of PS, number of prior regimens, or response to prior therapy. An additional 35% of patients in the erlotinib arm had stable disease, compared with 27% of patients in the placebo arm; the median duration of response was 7.9 months versus 3.7 months, and the PFS was 2.2 months versus 1.8 months (\( p < 0.001 \)). Based on this modest RR of 8.9% and overall disease control rate of approximately 45%, effecting the median survival seems unlikely, because usually more than 50% of patients must benefit more from an intervention to affect the median. However, the median was 6.7 months in the erlotinib arm versus 4.7 months in the placebo arm (\( p < 0.001 \)). Perhaps some patients who had progression as their best response were also benefited in some way. Toxicities were similar to all the previous trials using EGFR-TKIs, with predominance of rash and diarrhea, with 5% of patients discontinuing therapy. The incidence of pneumonitis was equal in both groups. Erlotinib had a beneficial effect on survival in almost all subgroups tested, although never-smoking status was the factor most predictive of survival gains. Tumor biopsy samples from the study participants were used to determine whether responsiveness to erlotinib was influenced by the status of EGFR expression, the number of EGFR copies, or the presence of EGFR mutations. The authors concluded that expression of EGFR and an increased number of copies of EGFR were predictive of survival, whereas EGFR mutational analysis was not. Despite these findings, the timing of erlotinib in the salvage setting remains undefined. The interactions between clinical and molecular parameters were comparable between both agents (table 1), but there were significant differences in the toxicity profiles (table 2). Significantly more patients in the docetaxel arm experienced grade 3/4 neutropenia (40.2% versus 5.35%; \( p < 0.001 \)), neutropenic fever (12.7% versus 1.9%; \( p < 0.001 \)), and infection with neutropenia (3.3% versus 0%; \( p < 0.004 \)). More patients in the docetaxel arm required hospitalization and the use of growth factor support. Grade 3/4 non-hematologic toxicities were similar in the two arms except for a higher rate of alopecia in the docetaxel arm and higher rates of ALT elevation in the pemetrexed arm. When considering all grades of toxicity, more patients in the docetaxel arm also experienced higher rates of diarrhea and neurosensory toxicities. Both agents result in very low rates of grade 3/4 nausea, but a substantial number of patients do experience grade 1 or 2 nausea. Because grade 1/2 nausea is unpleasant for the patients, one must consider the use of prophylactic 5HT3 antagonists for both agents.

**Table 3. Efficacy of gefitinib and erlotinib in phase III studies of NSCLC**

<table>
<thead>
<tr>
<th></th>
<th>Thatcher et al.(^{23})</th>
<th>Shepherd et al.(^{24})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gefitinib</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250 mg/day</td>
<td>8%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Placebo</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Erlotinib</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 mg/day</td>
<td>32%</td>
<td>35%</td>
</tr>
<tr>
<td>Placebo</td>
<td>31%</td>
<td>27%</td>
</tr>
<tr>
<td><strong>TTP</strong></td>
<td>3 months</td>
<td>2.2 months</td>
</tr>
<tr>
<td></td>
<td>2.6 months</td>
<td>1.8 months</td>
</tr>
<tr>
<td><strong>MST</strong></td>
<td>5.6 months</td>
<td>6.7 months</td>
</tr>
<tr>
<td></td>
<td>5.1 months</td>
<td>4.7 months</td>
</tr>
<tr>
<td><strong>1-year survival</strong></td>
<td>27%</td>
<td>31.2%</td>
</tr>
<tr>
<td></td>
<td>21%</td>
<td>21.5%</td>
</tr>
</tbody>
</table>

RR, response rate; SD, stable disease; TTP, time to progression; MST, median survival time.
factors in determining the optimal sequence in which it can be used with chemotherapy are still under investigation.

Why was erlotinib superior to placebo in a randomized phase III study but gefitinib was not? One could speculate that the dose of 150 mg of erlotinib is sufficient to effect greater numbers of patients compared with 250 mg of gefitinib. Indeed, 150 mg of erlotinib is equivalent to approximately 700 mg of gefitinib. Perhaps the higher dose of erlotinib allowed for inhibition of some tumors with wild type EGFR, whereas the lower dose of gefitinib was sufficient to inhibit only mutated EGFR. Perhaps the disparate results were the result of patient selection or chance alone. The confidence intervals for survival do overlap. Interestingly, the placebo arm of the erlotinib study performed worse than the placebo arm of the gefitinib study (Table 3). Another plausible explanation is that erlotinib is a slightly more effective drug than gefitinib. One must be careful, however, when declaring one trial to be “positive” and another trial “negative.” In fact, the data with each agent seem nearly superimposable. Response rates, SD rates, and PFS seem very similar. One-year survival was approximately 30% for each agent, and the magnitude of change on the survival curves for each study is also quite similar. Both agents seem to benefit the same subgroups and are associated with a similar toxicity profile. Most patients who benefited with erlotinib might benefit similarly with gefitinib. Significant differences in the magnitude of toxicity are evident, however, as skin and gastrointestinal toxicities are dose-related.

Other Agents Tested in Phase III Studies

Topotecan is a water-soluble semisynthetic analogue of the alkaloidal camptothecin with activity against a wide range of tumors. It has a specific mechanism of action via inhibition of topoisomerase-1, resulting in damage during DNA replication and ultimately in tumor cell death.26 In the largest second-line trial to date, Ramla et al. randomized 829 patients with NSCLC with PD after one line of chemotherapy to oral topotecan 2.3 mg/m²/d on days 1 to 5 every 3 weeks versus docetaxel 75 mg/m² IV once every 3 weeks.37 The primary end point was survival with a non-inferiority design. Most patients were PS 0/1 (86% and 84%), and more than half of patients on each arm had progressed within 3 months of completing first-line therapy. Response rates were equal for both groups (5%), as was median survival (27.9 versus 30.7 weeks; log-rank p = 0.057) and time to progression (11.3 versus 13.1 weeks; log-rank p = 0.0196), in both cases numerically favoring the docetaxel arm. Despite this trend toward benefits with docetaxel, the study did meet its non-inferiority end point for topotecan. The rates of neutropenia were similar, but the incidence of anemia and thrombocytopenia were much higher for topotecan. Nausea, vomiting, and diarrhea were more common with topotecan, and neuropathy and alopecia were more common with docetaxel. The implications of these results on regulatory approval for topotecan are uncertain.

Combination Chemotherapy

Although several studies have demonstrated that the combination of agents is more effective than single-agent therapy in the first-line treatment of NSCLC, no randomized phase III trials have been reported in the second-line setting. Several single-arm trials and randomized phase II studies of combination chemotherapy have been undertaken. Takeda et al. randomized patients to docetaxel 60 mg/m² day 1 or docetaxel 60 mg/m² on day 8 with gemcitabine 800 mg/m² on days 1 and 8, both repeated every 3 weeks until progression.28 Sixty-five patients were enrolled, and the trial had to be terminated early because of an unexpectedly high incidence of interstitial lung disease and three treatment-related deaths in the docetaxel-gemcitabine arm. The MST and 1-year survival were similar in both groups. In a randomized phase II study of 130 patients with relapsed NSCLC, docetaxel 30 mg/m² plus irinotecan 60 mg/m² (day 1 and 8) were compared with docetaxel 75 mg/m² day 1, both repeated every 3 weeks.29 There were no significant differences in response rates (20% versus 14%), MST (6.5 versus 6.4 months), and 1-year survival (37% versus 34%). The rates of neutropenia and anemia were similar in both arms, but the combination arm had higher rates of diarrhea (12% versus 3%; p = 0.05) and thrombocytopenia (17% versus 6%; p = 0.04). Another study evaluated the combination of vinorelbine 25 mg/m² IV plus gemcitabine 800 mg/m² IV (both given on days 1 and 8) in 39 patients with NSCLC refractory or resistant to platinum- or taxane-based therapy.30 Only one patient had an objective response (2.6%), MST was 7.3 months, and 1-year survival was 35%. The main adverse event was febrile neutropenia, with a 13% incidence. Overall, these studies suggest that combination chemotherapy is not more effective than single-agent therapy, but it is associated with more toxicity. Until randomized trials demonstrate improved efficacy for combination therapy, single-agent therapy should remain standard.

Newer Strategies

Angiogenesis, the process of new blood vessel formation, plays an important role in both the growth and metastasis of NSCLC, making it an attractive target. Antiangiogenic drugs are currently being tested in clinical trials, both alone or combined with chemotherapy, including several trials in lung cancer. Confirmatory evidence of the benefits of bevacizumab in NSCLC was provided in a phase III trial (E4599) by Sandler et al.31 Patients in this study were randomized to receive carboplatin plus paclitaxel with or without bevacizumab. The bevacizumab arm showed improvement in response rates (27% versus 10%), time to progression (6.4 versus 4.5 months), and survival (12.5 versus 10.2 months) in the first-line setting.

Several small-molecule TKIs targeting different pathways important in angiogenesis have been developed. BAY 43-9006 (sorafenib) is a potent inhibitor of Raf-1 and active against VEGFR-2, VEGFR-3, and PDGFR-β.32 This agent has shown activity in multiple tumor types, including a recently published phase III trial in advanced renal cell carcinoma.33 The most common adverse events seen are skin rash and hand and foot syndrome. The Eastern Cooperative Oncology Group (ECOG) is currently enrolling patients in a phase II clinical trial of sorafenib in refractory NSCLC. SU11248 (sunitinib) is a selective inhibitor of several protein
tyrosine kinases, including VEGF-R types 1 to 3, PDGFR-α, and PDGFR-β, which has also shown activity in renal cancer,\(^\text{34}\) as well as in imatinib-resistant gastrointestinal stromal tumor.\(^\text{35}\) Both of these agents have been recently approved by the United States FDA, suntet for use in metastatic renal cell carcinoma and gastrointestinal stromal tumor, and sorafenib for use in metastatic renal cell carcinoma.

Cetuximab is a chimeric antibody of the immunoglobulin G1 subclass that targets and blocks the human EGFR.\(^\text{36}\) Cetuximab blocks the binding of EGF and TGF-α to EGFR and inhibits ligand-induced activation of the receptor. Cetuximab also stimulates EGFR internalization, effectively removing the receptor from the cell surface for interaction with the ligand, which may contribute to the inhibitory effects of this antibody.\(^\text{37}\) Multiple studies have combined cetuximab with chemotherapy in the first- and second-line setting.\(^\text{38-41}\) These studies have shown enhanced responses and/or improved survival compared with historical controls, with skin rash being the most common toxicity reported. Lilenbaum et al.\(^\text{42}\) have reported their experience with single-agent cetuximab in the second-line setting. In this phase II clinical trial, 66 patients with recurrent or metastatic IIIb/IV NSCLC treated with at least one previous regimen were treated with cetuximab 400 mg/m\(^2\) on day 1, followed by 250 mg/m\(^2\) weekly until disease progression or unacceptable toxicity. Three patients had an objective response (3.3%), and MST was 8.1 months. Given the interesting ability of cetuximab to resensitize cells to drugs to which they have become resistant (in head/neck cancer and colon cancer), similar strategies are being tested in NSCLC, including a Hoosier Oncology Group dose escalation study of pemetrexed plus cetuximab and an ongoing Imclone-run trial of pemetrexed or docetaxel with or without cetuximab.

There is strong preclinical evidence to support simultaneous blockade of VEGF and the EGFR pathways. The EGFR also seems to regulate VEGF,\(^\text{43,44}\) and several studies have demonstrated that blockade of the EGFR results in an antiangiogenic effect.\(^\text{45,46}\) Furthermore, data suggest that an increased production of VEGF represents one mechanism by which tumor cells escape anti-EGFR monoclonal antibody therapy.\(^\text{27}\) A phase I/II study examined erlotinib and bevacizumab as second-line therapy in patients with non-squamous cell stage IIIb/IV NSCLC.\(^\text{48}\) In the phase I portion, erlotinib 150 mg/day orally plus bevacizumab 15 mg/kg IV every 21 days was established as the phase II dose, although no dose-limiting toxicities were observed. Of the 34 patients in phase II, eight had a response (20%), and the overall survival was an encouraging 12.6 months. A randomized trial comparing erlotinib with and without bevacizumab is being conducted.

CONCLUSIONS

There are currently three United States FDA-approved agents for the second-line treatment of NSCLC: docetaxel 75 mg/m\(^2\) every 3 weeks, pemetrexed 500 mg/m\(^2\) every 3 weeks, and erlotinib 150 mg orally daily. Based on the current available data, the efficacy is similar among agents in a general patient population, but there are significant differences in their toxicity profiles. The hematologic toxicity is greater for docetaxel versus pemetrexed and erlotinib. Non-hematologic toxicity, mainly rash and diarrhea, is greater for erlotinib. Erlotinib should be strongly considered as second-line treatment in never smokers who have not benefited from first-line chemotherapy. For smokers who have benefited from first-line chemotherapy and are maintaining a PS of 0 or 1, a trial of pemetrexed is reasonable. Most of the survival benefit for any agent is appreciated mainly in PS 0 and 1 patients, and a trial of each agent is warranted in patients maintaining a good PS.

REFERENCES