Perspectives on Salvage Therapy for Non–Small-Cell Lung Cancer

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Platinum-based chemotherapy offers a modest survival advantage over best supportive care in chemotherapy-naive patients with a good performance status and advanced/metastatic non–small-cell lung cancer (NSCLC). Despite the survival benefit associated with first-line chemotherapy, the majority of patients will experience relapse or disease progression. In clinical practice, an increasing number of patients maintain a good performance status after first-line treatment and are eligible for further treatments. Docetaxel (Taxotere) at 75 mg/m² given once every 3 weeks has been the standard of care for second-line chemotherapy since the year 2000. Pemetrexed (Alimta) is a novel multitargeted antifolate agent with single-agent activity in first- and second-line treatment of NSCLC. A large phase III study comparing docetaxel to pemetrexed in second-line therapy demonstrated that pemetrexed is equally active and less toxic than docetaxel. Based on these results, pemetrexed is a reasonable second-line chemotherapy option for patients with recurrent, advanced NSCLC. Progress made in the field of molecular biology has led to the identification of drugs active against specific cellular targets. Gefitinib (Iressa) and erlotinib (Tarceva) are both orally active tyrosine kinase inhibitors of the epidermal growth factor receptor. Phase II and III trials have demonstrated that these agents are active particularly in a subgroup of patients with specific biologic characteristics. Both drugs have been approved for the treatment of pretreated NSCLC. Other drugs, such as cetuximab (Erbitux) and bevacizumab (Avastin) have shown promising activity in NSCLC and are currently being tested in clinical trials.

Non–small-cell lung cancer (NSCLC) accounts for approximately 80% of all cases of lung cancer and is the leading cause of cancer death in the world.[1] NSCLC was long considered a poorly chemosensitive disease, and the role of systemic therapy was unclear. Since the publication of a meta-analysis in 1995, it has been accepted that platinum-based chemotherapy modestly but significantly prolongs survival and improves quality of life over best supportive care in patients with NSCLC.[2] Incorporation of newer active drugs (taxanes, gemcitabine [Gemzar], vinorelbine) has led to regimens that achieve higher response rates than older regimens, although not necessarily a survival advantage.[3] Randomized studies also showed that cisplatin-based chemotherapy and new chemotherapeutic agents result in improved quality of life compared with best supportive care.[4] More recently, phase III trials showed that two-drug regimens including a platinum and one of the new cytotoxic agents offer an improved response and survival rate compared with a single agent,[5,6] whereas three-drug regimens do not improve survival in advanced disease.[7] Despite the survival benefit associated with first-line chemotherapy, the majority of patients will experience relapse or disease progression. Because of improved therapeutic results with newer agents and supportive therapies, an increasing number of patients maintain a good performance status after first-line treatment and are eligible for further treatment. In this review, we summarize the published results of second-line treatment in NSCLC and discuss future strategies.
Second-Line Therapy in NSCLC:

**Standard Options** Recent studies have demonstrated that several new chemotherapy agents may be useful for the treatment of refractory or recurrent NSCLC after initial platinum-based chemotherapy. Results obtained with docetaxel (Taxotere),[8,9] pemetrexed (Alimta),[10] gefitinib (Iressa),[11] and erlotinib (Tarceva) are particularly consistent.[12] Table 1 summarizes the results obtained with these agents in previously treated patients.

**Docetaxel**

Four phase II trials showed that docetaxel was active in pretreated NSCLC patients. When used as a single agent, docetaxel (100 mg/m$^2$ every 3 weeks) provided response rates ranging from 16% to 22%, with grade 3/4 neutropenia (National Cancer Institute Common Toxicity Criteria, NCI-CTC) being the primary dose-limiting event.[13-16] In a phase II study conducted by Fossella et al in platinum-refractory NSCLC, the response rate was 21% and median survival was 42 weeks.[14] These promising results led to two large phase III trials that established docetaxel as the first chemotherapeutic agent with proven benefit for patients with recurrent or refractory disease following platinum-based first-line chemotherapy.[8,9] In the TAX 320 trial, 373 NSCLC patients showing disease progression after platinum-based chemotherapy were randomly assigned to docetaxel or to a control arm of vinorelbine or ifosfamide.[8] The response rate was significantly higher in the group of patients treated with docetaxel (11% for those treated with 100 mg/m$^2$, and 7% for those treated with 75 mg/m$^2$) than in the group treated with navelbine or ifosfamide (1%). Importantly, overall survival was initially similar between the two arms, but the survival analysis was censored when additional poststudy chemotherapy was administered, and the 1-year survival rate proved significantly higher in the docetaxel arm (32% vs 10%, $P < .01$). Quality-of-life analysis measured using the Lung Cancer Symptom Scale demonstrated a significant improvement in quality of life for patients treated with docetaxel.[17] In another phase III trial, Shepherd et al randomly allocated 104 NSCLC patients pretreated with platinum-based chemotherapy to docetaxel, 100 mg/m$^2$, or best supportive care.[9] Because of the excess toxicity observed in the docetaxel arm, the drug dose was reduced to 75 mg/m$^2$ in the second half of the trial. Time to progression was longer for docetaxel patients than for best supportive care patients (10.6 vs 6.7 weeks, respectively, $P < .001$), as was median survival (7.0 vs 4.6 months, $P = .047$). The difference was more significant for patients receiving docetaxel, 75 mg/m$^2$, compared with corresponding best supportive care patients (7.5 vs 4.6 months, $P = .01$). Importantly, the fraction of patients alive at 1 year was significantly higher in the docetaxel group (37% vs 11%, $P = .003$). This study demonstrated that treatment with docetaxel was associated with significant prolongation of survival, and at a dose of 75 mg/m$^2$, the benefits of docetaxel therapy outweigh the risks. It is also interesting to note that the response rate obtained with docetaxel was only 7%. Although the expected response rate is low, the benefit in 1-year survival and the quality-of-life improvement justify docetaxel use in pretreated patients. At the present time, docetaxel (75 mg/m$^2$ every 3 weeks) is considered the standard regimen to which other experimental schedules should be compared. In order to identify a less toxic schedule, French investigators conducted a randomized phase II study comparing docetaxel at the standard every-3-week schedule with docetaxel at a weekly dose of 40 mg/m$^2$, in patients who had failed after first-line platinum-based chemotherapy.[18] This study, conducted in 125 advanced NSCLC patients, showed a significantly lower rate of severe neutropenia in the weekly arm, with comparable efficacy in terms of survival (5 months for both arms). These results suggested that the weekly regimen could be considered as a good alternative for patients at risk for severe neutropenia. Recent phase III trials suggested that non-platinum-based doublets may be equivalent to platinum doublets in terms
of efficacy. These data suggest that non-platinum-based combinations, including docetaxel-based regimens, should be explored in the second-line setting. Two recent randomized phase II trials compared docetaxel, 75 mg/m<sup>2</sup> every 3 weeks, to docetaxel/irinotecan (Camptosar).[20,21] Both trials showed that the addition of irinotecan to docetaxel failed to improve response rate or survival, while increasing gastrointestinal toxicity. Therefore, docetaxel-based two-drug combinations are not recommended as second-line therapy outside of the clinical trial setting. **Pemetrexed**

Pemetrexed is a novel antimetabolite that inhibits at least three enzymes - thymidilate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase - involved in the folate pathway.[22,23] As a single agent, pemetrexed has been evaluated in both first- and second-line therapy in patients with advanced NSCLC. In the two trials that evaluated the drug as first-line therapy, response rates ranged from 16% to 23%, and median survival was 9.6 and 8.4 months.[24,25] These results were comparable to those obtained for single-agent studies of agents with established activity in NSCLC, supporting further evaluation of pemetrexed as first-line therapy in association with a platinum drug. In a phase II trial, Smit et al evaluated activity and tolerability of pemetrexed in 81 NSCLC patients progressing during or within 3 months after first-line chemotherapy.[26] The response rate was 4.5% in platinum-pretreated patients and 14.1% in non-platinum-pretreated patients, with an overall median survival of 5.7 months. On the basis of the activity seen in this second-line study, a randomized phase III trial comparing single-agent pemetrexed with single-agent docetaxel as second-line chemotherapy was undertaken. In this study, patients received folate and vitamin B12 supplementation, in light of evidence that pemetrexed therapy without supplementation results in a significantly higher incidence of hematologic and nonhematologic toxicity.[27] A total of 571 NSCLC patients who had relapsed or progressed after first-line chemotherapy were randomly assigned to pemetrexed, 500 mg/m<sup>2</sup> every 21 days, or docetaxel, 75 mg/m<sup>2</sup> every 21 days.[10] No difference was observed in response rate (9.1% vs 8.8%, \( P = .10 \)) or in survival (median survival = 8.3 vs 7.9 months; 1-year survival = 29.7% in both groups; hazard ratio \( [HR] = 0.99 \)) between pemetrexed and docetaxel recipients, respectively. Patients receiving docetaxel were more likely to have grade 3/4 neutropenia (40.2% vs 5.3%, \( P < .001 \)), febrile neutropenia (12.7% vs 1.9%, \( P < .001 \)), neutropenia with infections (3.3% vs 0%, \( P = .004 \)), hospitalizations for neutropenic fever (13.4% vs 1.5%, \( P < .001 \)), hospitalizations due to other drug-related adverse events (10.5% vs 6.4%, \( P = .092 \)), use of granulocyte colony-stimulating factor (G-CSF, Neupogen) support (19.2% vs 2.6%, \( P < .001 \)), and all-grade alopecia (37.7% vs 6.4%, \( P < .001 \)), compared with patients receiving pemetrexed. Based on these findings, in August 2004, the US Food and Drug Administration (FDA) approved pemetrexed for the second-line treatment of advanced NSCLC. **Tyrosine Kinase Inhibitors**

Epidermal growth factor receptor (EGFR) is the target for cancer therapies such as gefitinib or erlotinib, which inhibit the tyrosine kinase activity of EGFR by reversibly competing with adenosine triphosphate (ATP) at the ATP-binding site within the EGFR protein. Both drugs are orally active, selective EGFR tyrosine kinase inhibitors (TKIs) that have demonstrated antitumor activity against a variety of human cancer cell lines expressing EGFR, including NSCLC.[28,29] Phase I studies, evaluating the safety and tolerability of gefitinib, identified rash and diarrhea as unique, dose-related toxicities. Of note, an 11% response rate has been observed among the 100 NSCLC patients enrolled in these trials.[30]
The negative results of the ISEL trial clearly indicate that it is not reasonable to propose TKI therapy for all patients with NSCLC, and targeted therapies should be offered only to patients presenting the biologic characteristics that predict sensitivity (Table 2). All trials conducted with TKIs to date have shown that some clinical characteristics are significantly associated with response to the treatment (eg, female gender, adenocarcinoma histology, and never-smoking history). These features are related to TKI sensitivity because they are significantly associated with biologic predictors of response. It is now clear that patients carrying specific EGFR gene mutations[34,35] or amplifications[36]-producing activation of antiapoptotic EGFR-dependent pathways[37]-are more sensitive to the drug. Further prospective trials should be conducted in patients selected for these biologic characteristics.

- **Erlotinib**-Paralleling the experience with gefitinib, erlotinib demonstrated activity in the second-line setting, but first-line trials showed no advantage to erlotinib in conjunction with standard chemotherapy.[38,39] On November 20, 2004, the FDA approved erlotinib for the treatment of patients with advanced NSCLC pretreated with standard chemotherapy. The FDA based this decision on results from a randomized double-blind, placebo-controlled pivotal phase III trial of patients with second- or third-line advanced NSCLC.[12] In this study, patients receiving erlotinib had a median survival of 6.7 months, compared to 4.7 months in patients who received placebo—a 42.5% improvement. A hazard ratio of 0.73 and a P value less than .001 were determined for comparisons of overall survival. In addition, 31.2% of patients receiving erlotinib in the study were alive at 1 year vs 21.5% in the placebo arm. Although the difference in the results obtained with gefitinib and erlotinib could be related to differences between these two drugs, it is possible that these conflicting results are due to the fact that the trial populations were not selected for any clinical or biologic characteristics. In the era of targeted therapies, it is not possible to treat all patients similarly, and the identification of individuals more likely to benefit from a particular treatment is of crucial importance.

**Other Cytotoxic Agents** Several drugs active against NSCLC, including gemcitabine and paclitaxel, have been evaluated in phase II trials, but results obtained with these compounds did not merit phase III testing. **Gemcitabine** Results reported with gemcitabine are conflicting. Nine phase II trials, evaluating activity and tolerability of gemcitabine in single-agent therapy, demonstrated response rates ranging from 0% to 21%.[40-48] Rosvold evaluated the activity of gemcitabine as second-line chemotherapy in 28 patients with advanced NSCLC progressing after prior carboplatin plus paclitaxel. This small phase II trial showed that gemcitabine is an active, well tolerated salvage regimen inpatients failing carboplatin-plus-paclitaxel first-line chemotherapy, producing a 21% objective response rate.[48] An Italian phase II trial tested gemcitabine as a single agent in 83 pretreated patients with advanced NSCLC. In this study, patients received gemcitabine at 1,000 mg/m² once a week for 3 weeks every 28 days. Sixteen patients (19%) achieved a partial response to treatment; the median duration of response was 29 weeks. Treatment was well tolerated. In this experience, gemcitabine showed significant activity without relevant toxicity, mainly in patients who were previously responsive to...
chemotherapy. Several trials evaluated the activity of gemcitabine in combination with other drugs in pretreated NSCLC patients. When combined with etoposide or topotecan (Hycamtin), gemcitabine obtained response rates of 21% [49] and 15%, [50] respectively. Five trials studied the combination of gemcitabine plus vinorelbine and showed response rates of 6% to 21%. [51-55] More recently, the combination of gemcitabine and docetaxel has been evaluated in a phase II trial conducted in 43 NSCLC patients relapsing after paclitaxel plus platinum-based chemotherapy. [56] In this trial, gemcitabine was administered at a dose of 1,000 mg/m² on days 1 to 8 followed by docetaxel, 100 mg/m² on day 1, recycled every 21 days. The combination proved to be active in terms of response rate (33%), median time to progression (6 months), and median survival (8 months), with an encouraging 28% 1-year-survival. Because of these conflicting results, no phase III trial has been conducted to compare gemcitabine to best supportive care or docetaxel in pretreated NSCLC. At the present time, the use of gemcitabine alone or in combination with other drugs is not recommended in previously treated patients.

**Paclitaxel**

Paclitaxel has also been studied in the second-line setting. Sculier et al. [57] conducted a phase II trial in patients who had failed first-line chemotherapy with platinum derivatives and/or ifosfamide, by administering paclitaxel at a dose of 225 mg/m² given IV over 3 hours every 3 weeks. Although tolerance was acceptable, only two partial responses (3%) were observed, median survival was 4.5 months, and 1-year survival was 19%. In another multicenter trial, Socinski et al. [58] sought to determine the activity of second-line, low-dose, weekly paclitaxel (80 mg/m²) in 62 patients with advanced NSCLC who failed first-line chemotherapy with carboplatin plus paclitaxel. The response rate was 8% and median survival, 5.2 months. The toxicity profile was extremely favorable, with the exception of mild-to-moderate neuropathy in 10% of the patients. In another phase II trial, 24 advanced NSCLC patients previously treated with platinum-containing regimens [59] received 60 or 90 mg/m² of paclitaxel (1-hour infusion for 6 consecutive weeks followed by 2 weeks without treatment for an 8-week cycle). Seven patients (29%) achieved a partial response and five (21%) had stable disease. Spanish investigators [60] administered weekly paclitaxel, 80 mg/m² as a 1-hour infusion, to 40 NSCLC patients who had been previously treated with platinumbased chemotherapy. The overall response rate was 37.5%, with 2 complete and 13 partial responses; the median survival was 9.7 months and the median time to progression, 5.4 months. Although these results seem to be comparable to those obtained with docetaxel, no direct comparison has been made, and the use of paclitaxel in the second-line setting is not recommended in clinical practice.

**Novel Agents**

Several new agents have proven active against NSCLC (Table 3). Cetuximab (Erbitux) is a monoclonal antibody that inhibits EGFR ligand binding, resulting in cell-cycle arrest and increased expression of proapoptotic proteins. Additive or synergistic growth inhibition was observed when cetuximab was combined with radiotherapy or chemotherapy in several preclinical models. [61-65] Recently, Rosell et al conducted a randomized phase II study comparing cetuximab/ cisplatin/vinorelbine vs cisplatin/vinorelbine as first-line treatment in 86 NSCLC patients who were immunohistochemically positive for EGFR expression. [66] This study suggested that cetuximab can be safely combined with chemotherapy to enhance activity. A large phase III trial comparing the cisplatin/vinorelbine/cetuximab combination vs chemotherapy alone as first-line therapy is ongoing. Bevacizumab (Avastin) is a monoclonal antibody directed against vascular endothelial growth factor (VEGF). The drug has been evaluated in a three-arm multicenter trial, [67] in which 99 patients with advanced NSCLC were randomized to standard chemotherapy with carboplatin plus paclitaxel or the same chemotherapy combination plus two different bevacizumab doses (7.5 and 15 mg/kg). The response rate increased by about 10% with bevacizumab, and time to progression was prolonged by about 3 months (from 4.5 to 7.5 months). However, six patients developed severe hemoptysis, and four toxic deaths occurred. A subset analysis of non-squamous cell NSCLC patients evaluated the impact of bevacizumab on overall response rate, time to progression, and median survival. This analysis showed that bevacizumab may prolong survival in non-squamous cell NSCLC patients without engendering unacceptable toxicity or an excess of toxic deaths. Objective response rate (32% vs 12%) and time to progression (30 vs 17 weeks) favored patients on bevacizumab. The Eastern Cooperative Oncology Group carried out a confirmatory phase III trial, in which patients with non-squamous cell NSCLC were randomized to carboplatin plus paclitaxel alone or combined with bevacizumab at 15 mg/kg. [Editor's note: ECOG 4599 was reported at ASCO 2005; see page 1000 for discussion.] Xenograft experiments performed in various tumor types suggest that growth inhibition using bevacizumab in combination with the TKI erlotinib is greater than with either agent alone. Sandler et al recently presented results of a phase I/II trial evaluating the combination of bevacizumab and erlotinib in 40 NSCLC pretreated with at least one prior chemotherapy regimen. [68] In this study, the response rate was 17.5%, and median survival was 9.3 months.
encouraging antitumor activity and favorable toxicity profile support further development of this combination for advanced NSCLC. Although results obtained with cetuximab and bevacizumab are encouraging, at the present time, their use is not recommended outside clinical trials.

**Table 3**

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<th>Novel Therapies for Non–Small-Cell Lung Cancer</th>
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**Conclusions**

Although several drugs are now available for the treatment of relapsed NSCLC, results are disappointing and any survival gain remains modest. Targeted therapies, such as EGFR-TKIs, have been shown to be active in a small group of patients with advanced NSCLC. The recent comprehension of the mechanisms underlying TKI activity allow us to select patients for such therapy, based on biologic predictors of sensitivity. Looking ahead, studies that correlate outcome to biologic end points will have the greatest ability to improve our understanding of lung cancer biology and the treatment of patients.

**Disclosures:**
The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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