Systemic Chemotherapy for Advanced Non-Small Cell Lung Cancer: Recent Advances and Future Directions

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Abstract
Systemic therapy improves the survival and quality of life of patients with advanced stage non-small cell lung cancer (NSCLC). Several new therapeutic options have emerged for advanced NSCLC, incorporating novel cytotoxic agents (taxanes, gemcitabine, pemetrexed) and molecular-targeted agents (erlotinib, bevacizumab). Efforts to improve the outcome of first-line therapy for advanced and metastatic NSCLC have primarily focused on the addition of targeted agents to platinum-based two-drug regimens. Bevacizumab, an antibody against vascular endothelial growth factor, is the first drug to demonstrate superior outcomes when added to systemic chemotherapy in advanced disease. Evaluation of the role of maintenance therapy following four to six cycles of first-line combination chemotherapy is ongoing. Both cytotoxic agents and targeted agents are suitable for evaluation in the maintenance setting. Promising results have been noted with single-agent paclitaxel as maintenance therapy following four cycles of combination therapy with carboplatin and paclitaxel. Phase III studies are now under way to evaluate the roles of gemcitabine, pemetrexed, and erlotinib as maintenance therapies for patients who experience a response or disease stabilization after four cycles of combination chemotherapy. Whether this approach will be successful in extending the survival of a select group of patients remains to be seen. The Oncologist 2008;13(suppl 1):5–13

Introduction
Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all cases of lung cancer, the leading cause of cancer-related death in both men and women in the U.S. Though there has been a gradual decline in the incidence of lung cancer in men, it continues to increase in women. More than 213,000 new cases will be diagnosed in the U.S. in 2007 [1]. A lack of effective screening tools for early detection, the presence of smoking-related comorbid illness, and the inherent molecular heterogeneity have all been impediments to research efforts to improve outcomes for patients with lung cancer.

The treatment of NSCLC is determined by disease stage. Surgery continues to be the mainstay of treatment for early-stage and localized disease. Multimodal therapy has become the norm for regionally advanced disease, and patients with advanced and metastatic disease are candidates for palliative chemotherapy, for which there is documented evidence of improvements in survival and quality of life measures. Systemic chemotherapy also benefits patients with earlier stages of the disease and has now become part of the multimodal therapeutic strategy for stages II and III NSCLC [2–5]. As a result, the development of novel systemic therapy regimens has become an impor-
tant focus of research efforts in NSCLC. With the notion that a “chemotherapy efficacy plateau” has been achieved with the present regimens, molecular-targeted drugs have entered the therapeutic arena in recent years [6, 7]. Agents that target the epidermal growth factor receptor (EGFR) and the angiogenesis pathway have proven to be efficacious in the management of NSCLC [6, 7]. Several other molecular targets are under evaluation as monotherapy or in combination with systemic chemotherapy.

**Treatment of Advanced-Stage NSCLC**

Approximately 40% of patients with NSCLC present at an advanced stage, including patients with metastatic disease and those with locally advanced disease with malignant pleural or pericardial effusion. Treatment options for these subgroups are chosen based on patient performance status (PS), because it is an important determinant of outcome [8]. Combination chemotherapy is considered the standard of care for patients with advanced NSCLC and a PS score of 0 or 1 [9]. Both platinum-based two-drug regimens and non-platinum combinations have been shown to be efficacious in the first-line treatment of advanced NSCLC [10–14].

Patients with a PS score of 2 have a poor prognosis, with a median survival time of approximately 4 months [15]. The optimal treatment strategy for patients with a PS score of 2 is yet to be defined, although there is greater use of single agents in this patient subset, especially in those with significant comorbid conditions. A reduction in PS as a result of an aggressive tumor warrants standard combination chemotherapy to achieve the best results.

**Platinum-Based Regimens**

The benefits of platinum-based combination chemotherapy over best supportive care (BSC) as first-line treatment for patients with advanced NSCLC were first reported in a randomized clinical trial published in 1988 [16]. Further evidence for the efficacy of platinum-based chemotherapy was provided by a meta-analysis of all available randomized clinical trials [17]. The analysis demonstrated that cisplatin-based chemotherapy was associated with a 10% greater 1-year survival rate (hazard ratio, 0.73). This led to the evaluation of several platinum-based combinations for the first-line treatment of advanced NSCLC.

Based on promising single-agent activity, newer agents such as the taxanes, gemcitabine, and vinorelbine have been combined with platinum compounds. Several randomized clinical trials have been conducted to evaluate cisplatin as monotherapy or in combination with a taxane, gemcitabine, or vinorelbine [18–20]. The two-drug combinations were proven to have superior efficacy, but at the expense of added toxicity. These studies provided further evidence in support of the use of cisplatin-based combinations for the first-line treatment of advanced NSCLC.

**Comparison of Platinum-Based Combinations**

The availability of several efficacious regimens led to the direct comparison of these combinations. A four-arm randomized phase III study, the Eastern Cooperative Oncology Group (ECOG) 1594 trial, was conducted to compare the efficacy and toxicity profile of cisplatin plus gemcitabine, cisplatin plus docetaxel, and carboplatin plus paclitaxel, with a reference regimen of cisplatin plus paclitaxel [10]. There was no difference in response rate, median survival time, or 1-year survival rate among the four regimens. However, cisplatin plus gemcitabine did confer a longer time to progression. Similar observations were made in the Southwest Oncology Group 9509 study and other randomized studies that compared various two-drug combinations (Table 1).

The efficacy of gemcitabine as a first-line treatment was initially established in two randomized trials. The combination of cisplatin plus gemcitabine was associated with higher survival and response rates than seen with cisplatin monotherapy in a phase III study that included 522 patients.

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<th>Table 1. Comparison of two-drug combinations</th>
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<td>Kelly et al. [11], SWOG 9509, n = 408</td>
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*p = .029.
with advanced NSCLC [19]. In another randomized study, cisplatin plus gemcitabine was compared with cisplatin plus etoposide as first-line therapy [21]. The response rate, the primary endpoint, was higher with cisplatin plus gemcitabine, and there was also a trend toward longer survival. Based on these studies, the cisplatin plus gemcitabine regimen has become a commonly used combination for advanced NSCLC.

Docetaxel, a semisynthetic taxane, has also been proven to be efficacious in combination with a platinum compound. The regimen of cisplatin plus docetaxel was compared with cisplatin plus vinorelbine and carboplatin plus docetaxel in a randomized phase III study (n = 1,218) [22]. The median and 2-year survival rates were superior for cisplatin plus docetaxel, while the carboplatin plus docetaxel regimen had efficacy similar to that of cisplatin plus vinorelbine. Both docetaxel-based regimens were associated with improvements in several symptomatic and quality-of-life indices when compared with cisplatin plus vinorelbine. These results formed the basis for the U.S. Food and Drug Administration (FDA) approval of the cisplatin plus docetaxel regimen.

In Japan, irinotecan has been extensively evaluated in combination with cisplatin for the treatment of advanced NSCLC [23, 24]. The combination was compared with carboplatin plus paclitaxel, cisplatin plus vinorelbine, and cisplatin plus gemcitabine in a four-arm, randomized clinical trial [25]. Similar to the results found in ECOG 1594, the study demonstrated comparable efficacies among the four regimens, and they were all well tolerated. As a result, the regimen of cisplatin plus irinotecan is used commonly in Japan for patients with advanced NSCLC.

Because several chemotherapy regimens have similar degrees of efficacy in advanced NSCLC, the choice of which to use is often made after considering factors such as schedule, toxicity profile, and cost. Efforts to individualize therapy based on molecular markers in the tumor that predict resistance to specific chemotherapeutic agents are under way. Excision repair cross complementing 1 (ERCC1) gene overexpression has been linked to resistance to platinum [26]. Therefore, a randomized study assigned patients to treatments based on ERCC1 mRNA levels in the tumor tissue at baseline [27]. Patients with low ERCC1 mRNA levels were treated with cisplatin plus docetaxel, whereas those with high levels were treated with gemcitabine plus docetaxel. Response rates with cisplatin plus docetaxel were higher in patients with low ERCC1 expression. Similarly, overexpression of the ribonucleotide reductase M1 (RRM1) gene has been linked to resistance to gemcitabine therapy [28]. A randomized phase II clinical trial demonstrated the feasibility of selecting therapy based on RRM1 expression, and reported high response rates with such a pharmacogenomic treatment selection (Simon G et al., personal communication). Based on these results, a confirmatory phase III study is in progress. Such novel and individualized strategies will lead to further optimization therapy in the foreseeable future.

## Carboplatin Versus Cisplatin

Carboplatin-based regimens are easy to administer in the outpatient setting and have favorable nonhematologic toxicity profiles compared with cisplatin-based regimens. Several studies have been conducted to compare carboplatin-based regimens with cisplatin-based combinations in the first-line treatment of advanced NSCLC [10, 22, 29]. While some studies have suggested a slight advantage to cisplatin-based regimens, it is unclear whether this counterbalances the higher degree of toxicity found. A meta-analysis of studies comparing cisplatin- and carboplatin-based regimens demonstrated a slightly longer survival time for regimens that included cisplatin with a newer agent [30]. This observation was confirmed in another meta-analysis that used individual patient data to compare the efficacy of cisplatin-based regimens with that of carboplatin-based regimens for advanced NSCLC [31]. Overall, there was a slightly higher response rate with cisplatin-based regimens. Though there was no significant survival difference, studies that used a third-generation agent (gemcitabine or a taxane) in combination with cisplatin yielded a slight advantage over carboplatin-based regimens. Because systemic chemotherapy is administered with the primary goal of palliation, the debate continues as to whether the marginal superiority of the cisplatin-based regimens justifies their use in routine patient care, given that the associated adverse events may have a negative effect on patient quality of life. In a curative setting, as is the case in the earlier stages of NSCLC (adjuvant therapy), cisplatin-based regimens may be preferred over carboplatin-based regimens. Carboplatin-based regimens are commonly used in the U.S., whereas cisplatin-based regimens are preferred in Europe for advanced NSCLC.

## Platinum Versus Nonplatinum Regimens

The use of nonplatinum regimens has been widely investigated with a view to improving the therapeutic index of chemotherapy for patients with advanced NSCLC. The advantage of excluding platinum compounds is that they are associated with considerable toxicity. Randomized trials that have directly compared platinum-based regimens with nonplatinum combinations have demonstrated comparable results [13, 14]. A recent randomized study compared carboplatin plus paclitaxel with carboplatin plus gemcitabine...
and the nonplatinum regimen of gemcitabine plus paclitaxel for advanced NSCLC [14]. All three regimens demonstrated comparable response rates and median survival times. Although the toxicity profiles were different in each arm, there was no clear advantage to the nonplatinum regimen. The observations were confirmed by a recent meta-analysis of all studies comparing platinum-based regimens with nonplatinum combinations, which demonstrated comparable 1-year survival rates [32]. Though the response rate was slightly higher with platinum-based regimens, so was the toxicity. Based on this, nonplatinum regimens are a reasonable choice for first-line therapy of advanced NSCLC and also represent an alternative option for patients who cannot tolerate platinum-based regimens.

**Strategies to Improve the Efficacy of Systemic Chemotherapy**

From the randomized trials that compared various platinum-based regimens, it became evident that a plateau in efficacy had been reached with the available agents for advanced NSCLC. Consequently, several novel approaches have been evaluated in an attempt to improve patient outcomes. One approach involved the evaluation of three-drug chemotherapy combinations in comparison with standard two-drug regimens [33]. There was no difference in efficacy with the addition of a third cytotoxic agent, and the toxicity profile was worse. This approach has subsequently been discarded. A comparison of platinum-based two-drug combinations with novel single-agent therapy demonstrated higher survival and response rates with the combination [34–35]. Thus, two-drug combinations form the foundation of systemic therapy for NSCLC.

Recent efforts have focused on the addition of a molecular-targeted agent to standard platinum-based combination regimens. The EGFR inhibitors have been the most extensively studied in combination with chemotherapy. Despite promising preclinical data in support of the combination regimens, phase III studies failed to demonstrate a survival advantage associated with the addition of an EGFR tyrosine kinase inhibitor (TKI) to systemic chemotherapy [36–38]. Monoclonal antibodies against EGFR, which have demonstrated intriguing activity in combination with chemotherapy in phase II studies [39, 40], are now undergoing phase III evaluation. Other targeted agents that have been tested in combination with chemotherapy, such as the matrix metalloproteinase inhibitors, farnesyl transferase inhibitors, and protein kinase C alpha inhibitors, have all shown efficacy greater than that seen with chemotherapy. These large negative trials have underscored the need for extensive preclinical evaluation of combination regimens before large phase III studies are launched, and also the importance of studying patient selection methods to identify molecular/clinical parameters that predict benefit from the targeted agent being evaluated.

More recently, bevacizumab, a monoclonal antibody against vascular endothelial growth factor, was demonstrated to lead to longer survival when administered in combination with chemotherapy [7]. The pivotal phase III study (ECOG 4599) randomized patients with advanced nonsquamous NSCLC to treatment with carboplatin plus paclitaxel alone or in combination with bevacizumab. Patients with squamous-cell histology, major hemoptysis, brain metastasis, or uncontrolled hypertension and those on therapeutic doses of anticoagulation were excluded because of concerns regarding the heightened risk of bleeding with bevacizumab. Following six cycles of therapy, patients in the experimental arm with a response or stable disease were given maintenance monotherapy with bevacizumab until disease progression or unacceptable toxicity. There were higher incidences of neutropenia, hypertension, hemorrhage, proteinuria, and treatment-related deaths with the three-drug regimen. Despite this, there was a longer overall survival time (12.3 months versus 10.3 months) and a higher response rate (35% versus 15%) with the addition of bevacizumab to carboplatin plus paclitaxel. Based on this study, bevacizumab has now been approved by the FDA for the first-line therapy of advanced nonsquamous NSCLC in combination with carboplatin plus paclitaxel. The results of ECOG 4599 were confirmed in a preliminary report of another phase III study (Avastin in Lung Cancer [AVAil], BO17704) that evaluated the regimen of cisplatin plus gemcitabine alone or in combination with one of two doses of bevacizumab (7.5 mg/kg or 15 mg/kg every 3 weeks) (Fig. 1) [42]. The formal presentation of the study results is awaited. It remains to be seen whether the lower dose of bevacizumab is regimen-specific (cisplatin plus gemcitabine) or will possess a degree of efficacy similar to the higher dose when combined with any regimen.

**Maintenance Therapy**

Following the use of bevacizumab as monotherapy after initial response or disease stabilization in ECOG 4599, it is now used in the maintenance setting for advanced NSCLC. This has led to an important debate regarding the role of maintenance therapy in advanced NSCLC. Until now, there has been no proven role for maintenance therapy because randomized clinical trials have failed to demonstrate any survival advantage for the continued administration of systemic chemotherapy beyond three to six cycles [43–46]. However, the available literature has several limitations that challenge the exclusion of maintenance therapy in NSCLC.
Smith et al. [43] conducted a randomized trial to compare the administration of mitomycin, vinblastine, and cisplatin for three cycles with administration for six cycles in patients with advanced NSCLC. Seventy-two percent of patients randomized to three cycles completed treatment, compared with 31% of patients randomized to six cycles. The median survival times and 1-year survival rates were similar for the two treatment arms. Furthermore, quality-of-life parameters were slightly better in patients randomized to three cycles. This study concluded that continuation of chemotherapy beyond three cycles was not associated with any additional advantage. In a similar study, Socinski et al. [44] randomized patients with advanced NSCLC to treatment with carboplatin and paclitaxel for four cycles or continuation of chemotherapy until disease progression or unacceptable toxicity. Interestingly, the median number of cycles received by patients in both arms of the study was four. There was no significant difference in response rate or overall survival time between the two treatment arms. Furthermore, quality-of-life parameters were slightly better in patients randomized to three cycles.

Weekly Paclitaxel as Maintenance Therapy

Belani et al. [47] conducted a randomized phase II clinical trial to evaluate the optimal schedule for weekly administration of paclitaxel in combination with carboplatin for advanced NSCLC. Patients were randomized to one of three different weekly schedules of paclitaxel. Following four cycles of therapy, patients who experienced a response or disease stabilization were then randomized to receive maintenance therapy with weekly paclitaxel or observation alone. Of the 401 patients who entered the study, 130 entered the maintenance phase. The data from this group of patients were pooled with the results of patients who received maintenance therapy with weekly paclitaxel in a phase III study that compared weekly and 3-weekly schedules of paclitaxel in combination with carboplatin [48]. Overall, 206 patients received maintenance therapy with paclitaxel from both studies. The outcome data were compared with those from patients who did not receive maintenance therapy [49]. Overall, the median survival time was 75 weeks in those using maintenance therapy, compared with 58 weeks in patients without maintenance therapy. Furthermore, maintenance therapy with weekly paclitaxel was well tolerated in both studies. Because the objective of these studies was not to establish the efficacy of maintenance therapy, the results of this analysis warrant prospective confirmation, but they are suggestive of the feasibility of prolonged administration of a less-toxic single agent as maintenance therapy for advanced NSCLC.

Docetaxel as Maintenance Therapy

Docetaxel is the only agent that is approved for both the first- and second-line treatment of advanced NSCLC. A recent study by Fidias et al. [50] demonstrated a potential role for docetaxel as maintenance therapy. In that study, patients with advanced NSCLC were treated with four cycles of carboplatin and gemcitabine. Patients who achieved a response or disease stabilization were randomized to treatment with docetaxel as maintenance therapy (early) or as salvage therapy at the time of disease progression (delayed). Of the 526 patients enrolled in the study, 231 were randomized after initial therapy. The overall response rate was higher for patients who received early docetaxel therapy than for those whose docetaxel was delayed (42% versus 6%). The survival data are awaited. The results are preliminary and limited by the small number of patients.
= 109) who were evaluable after randomization. Despite this, if the survival data favor the early docetaxel arm, this will serve as additional evidence in support of maintenance therapy for patients with advanced NSCLC.

**Gemcitabine as Maintenance Therapy**

The favorable tolerability profile of gemcitabine makes it an ideal choice for evaluation as maintenance therapy. Brodowicz et al. [51] conducted a phase III study to evaluate the role of gemcitabine in the maintenance setting. Patients with advanced NSCLC were treated with a combination of cisplatin plus gemcitabine for four cycles. Those patients showing a response or disease stabilization were subsequently randomized to maintenance therapy with gemcitabine or BSC. Of the 352 patients enrolled in the study, 206 were randomized in a 2:1 ratio to maintenance therapy or BSC. In this maintenance phase, the median time to progression was 3.6 months with gemcitabine, compared with 2 months with BSC ($p < .01$). Overall survival also favored the maintenance therapy arm (13 months versus 11 months; $p = .195$). A median of three cycles of gemcitabine was given as maintenance therapy. Approximately 18% of patients experienced objective responses during the maintenance phase of the study. One of the limitations of the study was that 42 patients who had disease stabilization or response in the initial phase did not enter the maintenance phase for various reasons. Furthermore, treatment delays were noted in 22% of patients randomized to gemcitabine maintenance. Despite these limitations, the study documents both feasibility and evidence of benefit in favor of gemcitabine as maintenance therapy. In order to evaluate this further, a randomized clinical trial is under way in the U.S. (Fig. 2). In that study, patients with advanced NSCLC are treated with four cycles of carboplatin plus gemcitabine combination therapy. Following the induction phase, patients with response or disease stabilization will be randomized to gemcitabine as maintenance therapy versus BSC alone. The study has an estimated sample size of 600 patients and enrollment is nearing completion (as of May 2007).

**Pemetrexed as Maintenance Therapy**

Pemetrexed is a multitargeted antifolate compound that has been approved for second-line therapy of advanced NSCLC. The approval was based on a study that compared pemetrexed with docetaxel in patients with advanced NSCLC who had progressed following prior platinum-based chemotherapy [52]. The efficacy results were similar for the two agents, but pemetrexed was associated with lower incidences of neutropenia, febrile neutropenia, and thrombocytopenia, and a lower hospitalization rate. The tolerability profile of pemetrexed is further improved by vitamin B12 and folic acid supplementation. Based on the results of this study, pemetrexed has now become a commonly used agent for second-line therapy of advanced NSCLC. The efficacy of pemetrexed is now being evaluated in the first-line treatment of advanced NSCLC (in combination with a platinum compound) and in combined-modality treatment of locally advanced NSCLC (in combination with a platinum compound and external-beam radiotherapy).

The favorable tolerability profile of pemetrexed also allows for its evaluation in the maintenance setting. In an ongoing randomized clinical trial, patients with advanced NSCLC who have stable disease or response following four cycles of platinum-based therapy are randomized in a 2:1 ratio to maintenance therapy with pemetrexed or placebo (Fig. 3). Maintenance therapy is continued until disease progression or unacceptable toxicity. All patients receive vitamin B12 and folic acid supplementation. The estimated

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**Figure 2.** Phase III trial (B9E-US-S194) of gemcitabine as maintenance therapy for advanced NSCLC: trial design.

Abbreviations: BSC, best supportive care; CR, complete response; NSCLC, non-small cell lung cancer; PD, progression of disease; PR, partial response; SD, stabilization of disease.
sample size is 660 patients. Because this is a potentially definitive study with survival as the primary endpoint, it is hoped that it will lead to a new paradigm for the treatment of advanced NSCLC.

**EGFR Inhibitors as Maintenance Therapy**

Erlotinib is an oral EGFR TKI. It is approved by the FDA for the treatment of advanced NSCLC following therapy with one or two prior chemotherapy regimens. The basis for this approval was a phase III study that demonstrated superior survival with erlotinib compared with placebo [6]. Gefitinib, another EGFR TKI, is associated with a response rate of approximately 10% in advanced NSCLC, but failed to demonstrate any survival advantage in a phase III study [53]. Both erlotinib and gefitinib have been studied in combination with chemotherapy for the first-line treatment of patients with advanced NSCLC, but the results were disappointing [36–38]. There was no survival advantage for the combination over chemotherapy alone. In these randomized trials, the EGFR TKI was continued as monotherapy following six cycles of combination therapy. Both erlotinib and gefitinib displayed a trend toward longer survival during the maintenance phase of the study [38, 54]. Based on these observations, a randomized clinical trial is under way to determine the utility of erlotinib as maintenance therapy following platinum-based chemotherapy (Fig. 4). Patients (n = 850) who show a response or disease stabilization after four cycles of combination chemotherapy will be randomized to erlotinib or placebo as maintenance therapy. The primary endpoint is progression-free survival. Study enrollment is ongoing (as of May 2007).

**Summary**

In addition to the evaluation of newer agents to improve the outcome for advanced NSCLC, maintenance therapy represents a novel strategy to increase the therapeutic potential of available agents. Several lines of evidence suggest that maintenance therapy with well-tolerated chemotherapeutic or molecular-targeted agents may benefit patients with advanced NSCLC. This idea also has the potential to improve the toxicity profile of combination chemotherapy by limiting it to four cycles. Because maintenance therapy uses currently available agents, it may also be associated with a better cost-to-benefit ratio. In the next 1–2 years, the results from several ongoing trials that focus on maintenance therapy will be available. It is hoped that the data will usher in a new treatment paradigm for patients with advanced stage NSCLC.
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