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Conclusion

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Key Words. Non-small cell lung carcinoma • Antineoplastic agents • Angiogenesis inhibitors
Protein kinase inhibitors • Antimetabolites

Disclosure: N.T. has received honoraria and research support from AstraZeneca, Sanofi-Aventis, Eli Lilly and Company, Merck, and Roche. P.B. has received honoraria from OSI/Genentech/Roche, Eli Lilly and Company, AstraZeneca, ImClone/BMS, and Sanofi-Aventis.

ABSTRACT

Chemotherapy for non-small cell lung cancer (NSCLC) can prolong survival and improve quality of life, but the majority of advanced stage patients succumb to disease within 2 years, meaning that there is room for improvement. The standard chemotherapy for NSCLC involves one of a number of chemotherapy doublets that have been shown to improve survival when compared with single agents or best supportive care. These doublets are generally comparable in terms of efficacy, differing primarily in their toxicity profiles. However, encouraging new options may be approaching, including therapies targeted to specific patient subpopulations, and the use of combinations of current and new drugs to produce synergistic effects.

Targeted therapies include the anti–epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib, EGFR monoclonal antibody cetuximab, and vascular endothelial growth factor (VEGF) inhibitors such as sorafenib, a small molecule TKI, and bevacizumab, a recombinant monoclonal VEGF antibody. Most attempts to combine EGFR-targeted therapies with standard chemotherapy in NSCLC have produced poor results, possibly as a result of antagonism between EGFR TKIs and chemotherapy. Positive results with bevacizumab suggest that VEGF- rather than EGFR-targeted therapies may produce better results when combined with chemotherapy.

Other new drugs being tested include enzastaurin, an oral serine threonine kinase inhibitor; vinflunine, a vinca alkaloid; dihydrofolate reductase inhibitors; and thymidylate synthase inhibitors.

Combinations of therapies, especially those acting via different mechanisms, hold promise for improvements in survival, but careful testing is required to determine optimum combinations of available drugs and where new drugs fit into the armamentarium. *The Oncologist* 2008;13(suppl 1):37–46

INTRODUCTION

A major theme that arises from this supplement is that while chemotherapy for non-small-cell lung cancer (NSCLC) prolongs survival and quality of life, the majority of advanced stage patients succumb to disease within 2 years, leaving room for improvement. The main chemotherapy doublets for untreated patients are comparable in terms of efficacy, distinct only in terms of somewhat differing safety profiles. The use of triplet chemotherapy does not result in further increased survival, but instead, increased toxicity. However, encouraging new options do seem to be on the horizon, including the targeting of therapies to specific patient subpopulations, and the use of combinations of current and new drugs to produce additive or synergistic effects.

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doi: 10.1634/theoncologist.13-S1-37

As such, the better we can understand prognostic and therapeutic predictive factors in NSCLC, the clearer the choice of optimum therapy becomes. Current studies are focusing on patient factors such as smoking history, histology, molecular characteristics such as mutation state, gene copy number, protein expression levels, mass spectrometry profiles, and response to any previous lines of therapy [1].

Patients previously thought to derive little gain from chemotherapy, such as those who are elderly and those with a performance status (PS) score of 2, may now receive the benefit of new agents, and these populations deserve more research with the aim of widening the treatment options. Additionally, maintenance therapy using well-tolerated chemotherapy or targeted agents may be beneficial in patients with advanced NSCLC.

First-line Treatment of NSCLC

Doublet Chemotherapy

Many chemotherapy doublets have been shown to improve survival when compared with single agents or no chemotherapy [2]. Commonly used first-line chemotherapy regimens in advanced NSCLC include carboplatin plus paclitaxel, cisplatin plus docetaxel, cisplatin or carboplatin plus gemcitabine, and cisplatin plus vinorelbine. While some phase III trials comparing platinum-based chemotherapy regimens have shown that taxane plus platinum combinations achieved higher response rates than with older chemotherapy combinations, a meta-analysis of 13 randomized trials using the standard regimens found no major differences in response rates or survival, although some toxicity benefits were seen with the cisplatin plus gemcitabine and cisplatin plus vinorelbine regimens [3]. A similar meta-analysis of time-to-event outcomes used data from >4,500 patients from 13 randomized trials to compare gemcitabine plus a platinum agent with any other platinum-containing regimen. Significantly lower overall mortality was observed with gemcitabine plus platinum regimens compared with other regimens (hazard ratio, 0.90; 95% confidence interval [CI], 0.84–0.96), with an absolute benefit at 1 year of 3.9%. The median survival time was 9.0 months for the gemcitabine plus platinum regimens and 8.2 months for the comparator regimens [4].

Cisplatin Versus Carboplatin

While some studies have demonstrated that cisplatin-based regimens result in a higher overall response rate in comparison with carboplatin-based regimens (relative risk 0.91, 95% CI, 0.84–0.99; $p = .02$), the 1-year survival rates for the two regimens are comparable (relative risk, 1.00; 95% CI, 0.94–1.07; $p = .93$) [5]. Indeed, research involving >3,000 patients failed to indicate a standard regimen [6]. Cisplatin-based chemotherapy tends to produce more frequent grade 3 or 4 nausea, vomiting, and nephrotoxicity, while carboplatin-based chemotherapy leads to more grade 3 or 4 thrombocytopenia [5]. A number of studies have demonstrated that carboplatin-based combinations offer generally similar efficacy but a better nonhematologic toxicity profile when compared with cisplatin-based combinations [7–10], although a recent individual patient data meta-analysis has suggested that cisplatin-based chemotherapy is marginally superior to carboplatin-based chemotherapy in terms of response rate, and in some subgroups, in extending survival, without producing more severe adverse effects [11].

New Doublets

A pemetrexed plus cisplatin combination in the first-line setting was used by both Shepherd et al. [12] (response rate, 45%; median survival time, 8.9 months) and Manegold et al. [13] (response rate, 39%; median survival time, 10.9 months). These promising data led to a randomized trial of gemcitabine plus cisplatin versus pemetrexed plus cisplatin, the results of which show that, for first-line treatment of advanced NSCLC, pemetrexed plus cisplatin provides similar efficacy with better tolerability and more convenient administration than gemcitabine plus cisplatin. In an analysis of survival by histologic groups, pemetrexed plus cisplatin had significantly better survival than gemcitabine plus cisplatin in adenocarcinoma and in large cell histology cases. In contrast, there was a (nonsignificant) trend toward better survival with gemcitabine plus cisplatin in squamous cell histology cases [14].

Pemetrexed has also been investigated in combination with carboplatin as a first-line treatment. Following a dose-ranging phase I study, two phase II trials have been completed using this combination. Zinner et al. [15] looked at the combination of pemetrexed plus carboplatin as a first-line treatment in 50 patients with advanced NSCLC, and reported a response rate of 24%, a 1-year survival rate of 56%, and a median survival time of 13.5 months. The switch from cisplatin to carboplatin did not appear to result in any reduction in efficacy; results compared favorably with those in the Shepherd et al. [12] and Manegold et al. [13] studies. Similarly, the combination of carboplatin plus pemetrexed showed median and 1-year survival measures comparable with those found in studies using cisplatin or carboplatin plus gemcitabine, carboplatin plus paclitaxel, and carboplatin plus docetaxel (12.2–14.2 months and 52%–62%, respectively) [16–19]. The pemetrexed plus carboplatin combination was well tolerated, with 26% of patients suffering grade 3 or 4 neutropenia and 2% throm-

bocytopenia, and only 6% having a grade 3 or 4 nonhematologic toxicity of any kind. Neuropathy and alopecia were mild, transient, and not cumulative.

Scagliotti et al. [20] randomly assigned patients with locally advanced or metastatic NSCLC to pemetrexed plus oxaliplatin or pemetrexed plus carboplatin. Of the 79 patients evaluable for tumor response, 60 (75.9%) achieved either a complete response, partial response, or stable disease, and response rates were similar for both treatment combinations. The median overall survival time was 10.5 months for both groups, 1-year survival rates were 49.9% and 43.9%, and median times to progression were 5.5 months and 5.7 months for pemetrexed plus oxaliplatin and pemetrexed plus carboplatin, respectively. The incidence of serious hematologic and nonhematologic toxicities was low compared with other platinum-based combinations [7, 10, 21, 22]. Grade 3 or 4 neutropenia, the most common toxicity, occurred in 7.3% of pemetrexed plus oxaliplatin patients and 25.6% of pemetrexed plus carboplatin patients. The most common nonhematologic toxicities were grade 3 vomiting (7.3% of pemetrexed plus oxaliplatin patients) and grade 3 fatigue (7.7% of pemetrexed plus carboplatin patients). From these data, it seems that combining pemetrexed with carboplatin is safe and effective in the first-line treatment of NSCLC, and that further investigation of the combination is justified.

Addition of Targeted Therapies

Erlotinib and Gefitinib

Most attempts to combine epidermal growth factor receptor (EGFR)-targeted therapies with standard cytotoxic chemotherapy in NSCLC have produced poor results. The Tarceva Responses in Conjunction with Paclitaxel and Carboplatin (TRIBUTE) trial [23] found that adding erlotinib, an EGFR tyrosine kinase inhibitor (TKI), to a standard carboplatin plus paclitaxel regimen did not confer any survival advantage over carboplatin plus paclitaxel alone in patients with previously untreated advanced NSCLC, although there was a survival benefit seen in patients who had never smoked (23 months versus 10 months in those receiving additional erlotinib and those using carboplatin plus paclitaxel alone, respectively) [24]. The negative survival effects in unselected, untreated patients were confirmed by the large phase III Tarceva Lung Cancer Investigation Trial (TALENT), which added erlotinib to cisplatin plus gemcitabine [25]. The two phase III Iressa NSCLC Trial Assessing Combination Therapy (INTACT) trials similarly found no survival benefit from adding gefitinib, another EGFR TKI, to platinum-based chemotherapy in unselected, untreated patients [26, 27].

Some recent studies have suggested that there may be antagonism between these EGFR TKIs and chemotherapy in tumor cells with wild-type *EGFR*. Preclinical data have shown that EGFR TKIs suppress cell growth/division as a result of G_1 cell cycle arrest in cell lines with wild-type *EGFR*. This reduces the cell cycle phase–dependent activity of chemotherapy. The majority of NSCLC tumors involve wild-type *EGFR*, and treatment order–specific interactions of combinations of an EGFR TKI plus chemotherapy could negatively affect the efficacy of these treatments [28]. These results have led to studies of alternating doses of chemotherapy and erlotinib, and erlotinib maintenance after chemotherapy, especially in patients with high *EGFR* gene copy numbers.

The combination of erlotinib plus pemetrexed is synergistic in NSCLC in vitro if exposure to erlotinib before pemetrexed is avoided, particularly in tumors sensitive to erlotinib, although this is independent of the mutation status of *EGFR* or K-*ras* genes. Exposure to erlotinib followed by pemetrexed is mostly antagonistic in erlotinib-sensitive cells and additive at best in erlotinib-resistant cells [29]. Based on these findings, a randomized phase II study is under way to compare progression-free survival (PFS) time using an intermittent combination of erlotinib plus pemetrexed with PFS time using pemetrexed alone in patients with recurrent NSCLC. A randomized phase II trial of erlotinib alternating with carboplatin and paclitaxel in the first-line treatment of NSCLC is also in progress [30].

Cetuximab

The chimeric anti-EGFR IgG_1 monoclonal antibody cetuximab has been approved for the second-line treatment of *EGFR*-expressing colorectal tumors and in squamous-cell head and neck carcinomas. It was shown to be effective in a small subset of NSCLC patients, although response does not necessarily seem to correlate with *EGFR* expression level, and it is unclear why some patients respond while other patients with tumors with high *EGFR* expression levels do not respond to cetuximab treatment [31].

A phase II study in chemotherapy-naïve patients with advanced NSCLC studied cetuximab in addition to cisplatin plus vinorelbine [32]. Patients were randomized to receive either cetuximab plus cisplatin plus vinorelbine ($n = 43$) or cisplatin plus vinorelbine alone ($n = 43$). The safety profile in both treatment arms was acceptable, with leukopenia being the most commonly reported toxicity. Patients in the chemotherapy-only arm had a lower overall response rate (20% versus 31.7%) than those treated with chemotherapy plus cetuximab, suggesting that adding cetuximab may improve the efficacy of cisplatin plus vinorelbine in first-line treatment of NSCLC. Another phase II trial treated che-

motherapy-naïve patients with stage IIIB/IV NSCLC with cetuximab plus docetaxel and carboplatin every 21 days for up to six cycles. Following this, patients with no evidence of disease progression were given cetuximab alone for 1 year or until disease progression. The response rate was 14.5%, with a median PFS time of 4.7 months and a median overall survival time of 11 months. Twenty-five patients received maintenance therapy with single-agent cetuximab (median treatment duration was 12 weeks) and this was well tolerated [33].

Cetuximab has also been studied in combination with gemcitabine-based doublets in a phase II trial enrolling previously untreated patients with stage IIIB/IV NSCLC irrespective of their *EGFR* status. Patients received cetuximab combined with either cisplatin plus gemcitabine or carboplatin plus gemcitabine. A control arm received the same chemotherapy regimen without cetuximab. Partial responses occurred in 18 patients (27.7%) in the cetuximab arm and 12 (18.2%) in the control arm. The median PFS times were 5.09 months and 4.21 months for the two arms, respectively; the median overall survival times were 11.99 and 9.26 months, respectively. Severe acneform rash was observed in 14.1% of patients in the cetuximab arm. Other toxicities were similar between the study arms [34].

However, disappointing results have recently been released from an open-label phase III study of cetuximab plus a taxane and carboplatin as first-line treatment for metastatic NSCLC in more than 600 patients from the U.S. and Canada. The study did not meet its primary endpoint of PFS, although secondary endpoints of the study, including response rate and PFS as assessed by clinical investigators, were statistically significant and favored the cetuximab arm. Further data from ongoing phase III trials, intended to be the pivotal studies for cetuximab NSCLC regulatory approval, are not yet available [35], although a preliminary press release has said that cetuximab combined with vinorelbine plus cisplatin met the primary endpoint of longer overall survival compared with chemotherapy alone in the phase III First-Line Treatment for Patients with EGFR-EXpressing Advanced NSCLC (FLEX) study [36]. Detailed results from this study are expected to be submitted for presentation at an upcoming conference.

Recent studies suggest that patients whose tumors have increased *EGFR* gene copy numbers detected by fluorescence in situ hybridization (FISH) benefit, while those with FISH-negative tumors do not [37, 38].

Sorafenib

Sorafenib is an oral multikinase inhibitor that inhibits the kinase activity of both C-Raf and B-Raf and targets the vascular endothelial growth factor (VEGF) receptor family (VEGFR-2 and VEGFR-3) and platelet-derived growth factor receptor family (PDGFR-β and stem cell factor receptor [Kit]). It is approved for the treatment of advanced renal cell carcinoma, but with its multiple targets it may also prove useful in other cancers.

The results of a phase II trial of sorafenib in NSCLC were recently reported. Patients with stage IIIB/IV NSCLC received sorafenib dosed at 400 mg twice daily. The study did not meet its initial efficacy criteria, with only one confirmed partial response in the first 20 patients, and was permanently closed after enrolling 25 evaluable patients. Of these, two are still receiving treatment (for 14 and 15 months). A total of three (12%) partial responses and seven (28%) patients with stable disease were observed in the 25 patients, and seven (28%) patients were progression free at 24 weeks. The median survival time and median time to progression were 8.8 and 2.9 months, respectively. No grade 3 or higher hematologic adverse events were observed, and 13 patients (52%) had a grade 3 nonhematologic adverse event, with fatigue (20%), diarrhea (8%), and dyspnea (8%) being the most common [39]. Another randomized phase II trial testing sorafenib plus gemcitabine versus sorafenib plus erlotinib as first-line therapy for NSCLC is now under way and is planned to enroll 100 patients: 58 patients aged ≥70 years old with PS scores of 0–2 and 42 patients aged <70 years old with PS scores of 2 [40].

A randomized, phase I/II, double-blind, multicenter trial of pemetrexed and carboplatin with or without sorafenib in the first-line treatment of patients with stage IIIB/IV NSCLC is currently recruiting patients [41], and a phase III trial of sorafenib in combination with carboplatin plus paclitaxel has been completed in untreated patients with stage IIIB/IV NSCLC: patients were randomized to receive treatment with carboplatin plus paclitaxel with or without sorafenib. The chemotherapy phase was followed by a maintenance phase where the patients can continue to receive sorafenib. The results from these trials will define what role sorafenib has in treating NSCLC [42].

Bevacizumab

Bevacizumab, a recombinant humanized monoclonal antibody to VEGF, is one of the most recent drugs to be approved in the U.S. and Europe for the first-line treatment of NSCLC. A trial evaluating bevacizumab in combination with carboplatin and paclitaxel versus chemotherapy alone in patients with advanced nonsquamous NSCLC reported a significant survival advantage in those randomized to bevacizumab plus chemotherapy (12.3 months versus 10.3 months in the bevacizumab and chemotherapy-alone arms, respectively) [43]. The response rate (35% versus 15%) and PFS time (6.2 months versus 4.5 months) were also better in

the bevacizumab arm. Recently, a confirmatory trial evaluating bevacizumab in combination with cisplatin and gemcitabine versus the same chemotherapy alone reported similar results, with bevacizumab conferring a longer PFS time and higher response rate [44]. The survival results from that trial are eagerly awaited. Various small phase II trials presented at the 2007 American Society of Clinical Oncology Annual Meeting have demonstrated that combining bevacizumab with standard chemotherapy regimens including docetaxel, pemetrexed, and platinum agents results in promising activity while remaining well tolerated [45, 46].

Similar results were reported recently by Patel et al. [47] using a three-agent combination of bevacizumab, pemetrexed, and carboplatin in 39 nonsquamous NSCLC patients: they reported a response rate of 59% and an overall survival rate of 54% at 18 months. The only grade 4 toxicities were diverticulitis and infection ($n = 1$ for each), and the maintenance section of the trial showed that the combination of pemetrexed plus bevacizumab appeared to favorably increase time to progression.

Another trial investigating the same treatment combination is ongoing and has recently reported preliminary results: nine of 12 enrolled patients continued to have disease control at a median duration of 20.2 weeks (range, 5–52 weeks), with five patients proceeding to maintenance treatment with bevacizumab. The authors concluded that their data demonstrated that adding bevacizumab to pemetrexed plus carboplatin was safe, well tolerated, and showed promising activity to date. The regimen was not associated with alopecia, neuropathy, or arthralgias/myalgias, and was conveniently administered. Enrollment in this trial is continuing [41].

This suggests that VEGF- rather than EGFR-targeted therapies may produce better results in combination with standard chemotherapy. Further research into these combinations is ongoing.

Second-Line Treatment of NSCLC

Docetaxel was approved for the second-line treatment of NSCLC after trials demonstrated a response rate of 17% and a median survival time of 8 months in pretreated patients. The standard 3-weekly dosing regimen has been challenged by a weekly schedule, and trials have shown that while weekly docetaxel does not result in better survival rates when compared with a 3-week docetaxel regimen, it does produce better compliance and response rates, and a lower rate of neutropenia [48–51].

Erlotinib is approved for the second- and third-line treatment of patients with locally advanced or metastatic NSCLC and has demonstrated longer survival compared with placebo after first- or second-line chemotherapy. It has been shown to produce a response rate of 8%–12%, regardless of type or number of prior chemotherapy regimens, and a median survival time of 6.7–8.4 months [52, 53]. Gefitinib is not available in Europe, but has been approved elsewhere internationally [54]. The use of gefitinib is currently limited in the U.S. and Canada to patients who are currently benefiting, or have previously benefited, from gefitinib treatment, or those involved in an access program [55]. This change was made after phase III studies demonstrated a lack of response (median survival time, 9.8 versus 9.9 months; 1-year survival rates, 41% versus 42% for the gefitinib 250 mg/day and placebo groups, respectively) compared with placebo or standard chemotherapy alone following gefitinib treatment except in the patient subgroups of never-smokers (no smoking history) and patients of Asian origin [26, 27, 56]. Analyses looking specifically at these subgroups showed significantly longer survival times in the gefitinib group than in the placebo group for never-smokers ($n = 375$; median survival time, 8.9 versus 6.1 months) and patients of Asian origin ($n = 342$; median survival time, 9.5 versus 5.5 months) [56]. Studies of Japanese and Chinese patients have shown much longer survival times and higher response rates compared with those observed with other chemotherapy regimens and compared with Western patients given gefitinib. For example, in 70 Japanese patients, the median survival time after second-line chemotherapy was 527 days, versus 175 days, with 1-year and 2-year survival rates of 59% versus 21% and 26% versus 16% for the gefitinib monotherapy and nongefitinib chemotherapy groups, respectively [57]. This preferential response to gefitinib is preserved in Asians living in a Western setting [58]. In addition, the phase III Iressa Survival Evaluation in Lung Cancer (ISEL) study has shown that high *EGFR* gene copy number was a predictor of clinical benefit from gefitinib, suggesting another population that should be studied further with this treatment [59].

Pemetrexed is now a commonly used agent for the second-line therapy of advanced NSCLC. The efficacy and toxicity of pemetrexed versus docetaxel was studied in patients with advanced NSCLC previously treated with chemotherapy. Treatment with pemetrexed resulted in clinically equivalent efficacy outcomes, but with significantly fewer side effects than with docetaxel [60]. It is therefore not surprising that it has been considered for combination with new targeted therapies in the second-line setting. In a small phase II trial, 36 PS score 0–1, nonsquamous NSCLC patients received pemetrexed (500 mg/m^2), oxaliplatin (120 mg/m^2), and bevacizumab (15 mg/kg) as second-line treatment for six cycles or until disease progression. Preliminary data included a median PFS time of 5.7 months and a median overall survival time of 15.0 months [61].

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