Carboplatin/Gemcitabine Combination in Advanced NSCLC

By Sakkaraiappan Ramalingam, MD and Chandra P. Belani, MD

The treatment of advanced non-small-cell lung cancer (NSCLC) has evolved rapidly over the past few years. Systemic chemotherapy is associated with both quality of life and modest survival benefit for patients with advanced NSCLC. Platinum-based doublet combinations are the “standard of care.” The US Food and Drug Administration (FDA) has approved gemcitabine (Gemzar), a pyrimidine analog, to be used in combination with cisplatin for the treatment of advanced NSCLC in the first-line setting. Randomized clinical trials have established comparable efficacy with improved therapeutic index for the carboplatin/gemcitabine regimen when compared with cisplatin/gemcitabine and other platinum doublets. Nonhematologic toxicities occur at a lower frequency with carboplatin/gemcitabine combinations compared with other “standard” platinum-based doublets, whereas dose-limiting thrombocytopenia, the most common toxicity, rarely requires therapeutic intervention. Both the 3- and 4-week schedules of carboplatin/gemcitabine result in similar efficacy and toxicity profiles, but the 3-week regimen is preferred. The combination of carboplatin and gemcitabine is an effective regimen with an acceptable toxicity profile for the treatment of advanced NSCLC. This regimen can also be used as a foundation for the development of innovative combinations with molecularly targeted agents.

Systemic chemotherapy prolongs survival and improves quality of life for patients with advanced non-small-cell lung cancer (NSCLC). Several randomized clinical trials conducted in the past few years have confirmed the efficacy of various platinum-based combination (cisplatin or carboplatin [Paraplatin]) regimens when used as first-line therapy for advanced NSCLC patients who have a good performance status (Eastern Cooperative Oncology Group [ECOG], performance status < 2). Platinum-based doublet regimens are superior to either single-agent therapy or threecombinations. While platinum compounds continue to hold their role as an essential component of the doublet regimens, the choice of the second agent is variable. Several third-generation chemotherapy agents, such as the taxanes (ie, paclitaxel, docetaxel [Taxotere]), gemcitabine (Gemzar), vinorelbine (Navelbine), and irinotecan (Camptosar), which possess efficacy as single agents for the treatment of advanced NSCLC, have been evaluated in combination with a platinum compound for first-line therapy. In fact, randomized trials have demonstrated comparable efficacy for combination regimens consisting of a platinum compound with any of the above-mentioned third-generation chemotherapy agents for the treatment of advanced NSCLC. These data provided the rationale for individualizing treatment for patients based on schedule of therapy, toxicity profile of the regimen, and cost. The role of the carboplatin/gemcitabine combination regimen for the treatment of advanced NSCLC is reviewed in this article.

Background

Carboplatin therapy results in lower incidences of nausea, vomiting, ototoxicity, and nephrotoxicity compared with cisplatin. Randomized trials comparing cisplatin-vs carboplatin-based regimens for the treatment of advanced NSCLC demonstrated comparable efficacy for both platinum compounds. Thus, based on its favorable toxicity profile, carboplatin has become the preferred platinum compound in the United States for the treatment of patients with advanced NSCLC, although cisplatin doublets are still preferred across the Atlantic. Gemcitabine is a novel pyrimidine analog that inhibits the enzyme ribonucleotide reductase that is essential for DNA synthesis. Multiple phase II trials have demonstrated the efficacy of gemcitabine as a single agent for the treatment of advanced NSCLC. In a randomized clinical trial, the combination of gemcitabine and cisplatin was superior to therapy with cisplatin alone. Subsequently, Schiller et al in the ECOG 1594 trial demonstrated comparable efficacy for the cisplatin/gemcitabine combination when compared with the control arm of cisplatin/paclitaxel. Cisplatin/docetaxel and carboplatin/paclitaxel were the other two arms of the ECOG 1594 study. Phase II studies with the carboplatin/gemcitabine regimen demonstrated response rates of 25% to 50% with overall median survival of 9.5 to 16 months. The regimen was well tolerated, with thrombocytopenia and neutropenia being the major toxicities; minimal nonhematologic side effects were seen. The efficacy was comparable to other commonly used doublet regimens and hence formed the basis to evaluate carboplatin/
gemcitabine in randomized trials for the treatment of advanced NSCLC.

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<th>Table 1</th>
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<td><strong>Carboplatin/Gemcitabine vs Cisplatin/Gemcitabine</strong> In Advanced Non–Small-Cell Lung Cancer</td>
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<td>Response rate</td>
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<td>1-yr survival</td>
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<td>Grade 3/4 thrombocytopenia</td>
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**Randomized Trials of Carboplatin/Gemcitabine** Rudd and colleagues with the London Lung Cancer Group compared the carboplatin/gemcitabine regimen with the combination of mitomycin (Mutamycin), ifosfamide (Ifex), and cisplatin (MIC) for the treatment of patients with advanced NSCLC. Both the regimens were administered every 3 weeks to patients with stage IIIB (pleural/pericardial effusion) or stage IV NSCLC.[10] Patients with an ECOG performance status of 0 to 2 were eligible for the study. The study enrolled 422 patients with previously untreated NSCLC. Although the response rates were similar between the two arms, the carboplatin/gemcitabine therapy was associated with superior survival over the MIC regimen (10.2 vs 6.8 months, \(P = .028\)). The incidence of grades 3/4 nausea (14% vs 5%), vomiting (10% vs 3%), constipation (7% vs 2%), and alopecia (9% vs 1%) were higher with the MIC regimen, while thrombocytopenia (25% vs 7%) occurred at a higher frequency in study patients receiving carboplatin/gemcitabine. In another study, the carboplatin/gemcitabine combination was compared with therapy using either the MIC regimen or the combination of mitomycin, vinblastine, and cisplatin.[23] The study included 372 chemonaive patients with advanced NSCLC who were not candidates for surgical resection or definitive radiotherapy. Carboplatin was given at an area under the concentration-time curve (AUC) of 5 (day 1) and gemcitabine was administered at 1,000 mg/m\(^2\) (days 1, 8, and 15). Treatment cycles were repeated every 28 days for the carboplatin/gemcitabine arm and every 3 weeks for the control arm. The response rate, median survival, and time to progression were similar between the two arms. No differences were noted between the two treatment arms in disease-related symptoms or quality-of-life benefit. Fewer inpatient stays were necessary for complications among the carboplatin/gemcitabine treated group. Grigorescu and colleagues conducted a randomized trial comparing the regimen of carboplatin/gemcitabine with cisplatin/vinblastine for patients with advanced NSCLC.[24] The study included 198 patients who were ≤ 70 years old and had an ECOG performance status of 0, 1, or 2. The response rate (27% vs 15%), median survival (11.6 vs 7.9 months, \(P = .0001\)), and 1-year survival rate (36% vs 13%, \(P < .05\)) were all significantly superior in the carboplatin/gemcitabine arm. The toxicity profiles were comparable between the two regimens. The efficacy noted with the carboplatin/gemcitabine combination with all of the randomized studies described above was comparable to the other "standard" platinum-based doublets used for the treatment of advanced NSCLC. Furthermore, the carboplatin/gemcitabine regimen was associated with minimal nonhematologic toxicities. Two randomized trials have compared the efficacy of the carboplatin/gemcitabine combination with that of the cisplatin/gemcitabine regimen (Table 1).[25,26] Zatloukal and colleagues randomized patients with advanced NSCLC to treatment with carboplatin at AUC 5, day 1, and gemcitabine, or therapy with cisplatin at 80 mg/m\(^2\), day 1, and gemcitabine. The dose of gemcitabine was identical for both the arms given at 1,200 mg/m\(^2\) on days 1 and 8. Both the regimens were administered on a 21-day schedule. The primary end point of the study was to assess toxicity between the two regimens, while the secondary end points included...
response rates, overall survival, and time to progression. The carboplatin arm was associated with a lower incidence of grades 3/4 nausea and vomiting (3.8% vs 16.2%, \( P = .0224 \)), and a higher incidence of thrombocytopenia (33% vs 16%, \( P = .0023 \)). The efficacy was comparable between the two arms with response rates of 47% and 48% for the carboplatin and cisplatin arms, respectively. The median survival was 8.1 months for patients on both the arms. In another study, Mazzanti et al randomized 115 patients to either cisplatin/ gemcitabine or carboplatin/ gemcitabine therapy.[26] In the cisplatin arm, gemcitabine was administered at a dose of 1,200 mg/m\(^2\) on days 1 and 8 while cisplatin was given at 80 mg/m\(^2\) on day 2. In the carboplatin arm, gemcitabine was given at a lower dose of 1,200 mg/m\(^2\) on days 1 and 8 while carboplatin was given at AUC 5 on day 2. The study demonstrated a lower incidence of nausea and vomiting with the carboplatin arm, while the overall survival was similar between the two arms (10 vs 11 months). Thus, the combination of carboplatin/gemcitabine results in comparable efficacy and a favorable toxicity profile when compared with the cisplatin/ gemcitabine combination.

### Carboplatin/Gemcitabine vs Single-Agent Gemcitabine

Sandler and colleagues demonstrated the superiority of the gemcitabine/ cisplatin combination over single-agent cisplatin in a randomized registration trial.[6] However, until recently, it was unclear whether the gemcitabine/platin combination was superior to single-agent gemcitabine. Sederholm and the Swedish Lung Cancer Study Group reported the results of a phase III study that compared the efficacy of carboplatin/ gemcitabine vs gemcitabine alone for the treatment of patients with advanced NSCLC (Table 2).[27] The study included 334 patients with advanced NSCLC who had an ECOG performance status of 0, 1, or 2. Patients were randomized to therapy with gemcitabine alone given at 1,250 mg/m\(^2\) on days 1 and 8, or in combination with carboplatin at AUC 5 on day 1. The response rate (30% vs 12%, \( P = .0001 \)), median survival (11 vs 9 months, \( P = .0024 \)), and 1-year survival rate (44% vs 32%) were superior with the doublet combination. The incidence of nonhematologic toxicity was comparable between the two arms. However, hematologic toxicity was more pronounced in the doublet arm. Grades 3/4 anemia, thrombocytopenia, and leukopenia occurred in 5%, 48%, and 32% with the doublet arm, respectively, compared with 2%, 4%, and 6% in the single-agent therapy arm, respectively. Thus, two-drug combinations are superior to singleagent therapy for the treatment of advanced NSCLC, though the benefit comes with some increase in toxicity.

### Table 2

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<thead>
<tr>
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<th>Carboplatin/Gemcitabine</th>
<th>Gemcitabine</th>
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<tbody>
<tr>
<td>N</td>
<td>164</td>
<td>170</td>
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<tr>
<td>Median number of cycles</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Grade 3/4 leukopenia</td>
<td>32%</td>
<td>6%</td>
</tr>
<tr>
<td>Grade 3/4 thrombocytopenia</td>
<td>48%</td>
<td>4%</td>
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<tr>
<td>Response rate</td>
<td>30%</td>
<td>12%</td>
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<tr>
<td>Median survival</td>
<td>11 mo</td>
<td>9 mo (( P = .0024 ))</td>
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<tr>
<td>Median TTP</td>
<td>6 mo</td>
<td>4 mo (( P = .0009 ))</td>
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<tr>
<td>1-yr survival</td>
<td>44%</td>
<td>32%</td>
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*Data from Sederholm.[27]*

TTP = time to progression.

### Carboplatin/Gemcitabine vs Nonplatinum Combinations

Nonplatinum regimens have been evaluated for the treatment of advanced NSCLC with the intention of reducing toxicities associated with platinum compounds. Studies have demonstrated a more favorable toxicity profile with nonplatinum doublets when used for the treatment of advanced NSCLC. However, it is unclear if the reduced toxicity comes at the price of reduction in efficacy. Randomized trials conducted to compare
the efficacy of platinum vs nonplatinum doublets have yielded mixed results thus far.[28,29] The Coalition of National Cancer Cooperative Groups is conducting a large randomized trial to compare the efficacy of the carboplatin/gemcitabine doublet with a nonplatinum doublet consisting of paclitaxel/gemcitabine (Figure 1) in chemonaive patients. The study also includes a third treatment arm receiving carboplatin/ paclitaxel. The treatment regimens were gemcitabine at 1,000 mg/m² on days 1 and 8 plus carboplatin at AUC 5.5 on day 1 vs gemcitabine at 1,000 mg/m², days 1 and 8, plus paclitaxel at 200 mg/m², day 1, compared to the control arm of carboplatin at AUC 6.0 plus paclitaxel at 225 mg/m², day 1. All three regimens were administered as 21-day cycles.

Figure 1: Schema—The Coalition of National Cancer Cooperative Groups Trial. AUC = area under the concentration-time curve; ECOG PS = Eastern Cooperative Oncology Group performance status; NSCLC = non–small-cell lung cancer. Data from Treat.[30]
Treat and colleagues recently presented the preliminary results of this study (Table 3),[30] with toxicity data from 534 accrued patients. The carboplatin/gemcitabine arm was associated with a higher incidence of grades 3/4 anemia and thrombocytopenia, while the incidence of grade 2 alopecia and neurosensory toxicities were lower. For the 345 patients in whom response data were available, comparable efficacy was noted for all three arms of the study. **Carboplatin/Gemcitabine: 3- vs 4-Week Schedule** Clinical trials performed with the carboplatin/gemcitabine combination initially used a 4-week regimen. Carboplatin was administered on day 1 of each cycle, and gemcitabine was given on days 1, 8, and 15. In these studies, it was noted that administration of the planned dose of gemcitabine on day 15 was limited by the occurrence of thrombocytopenia. Subsequently, 3-week schedules in which gemcitabine was administered on days 1 and 8 of every cycle were evaluated. Phase II studies with the 3-week regimen demonstrated comparable efficacy with the 4-week schedules. Two recent studies compared the two different schedules using the carboplatin/gemcitabine combination.[31,32] Masters and colleagues performed a randomized phase II trial of 100 chemonaive patients with advanced NSCLC (stage IIIB/IV).[32] In the 4-week arm, carboplatin at AUC 5 was administered on day 8 and gemcitabine at 1,100 mg/m[^2^] was given on days 1 and 8. In the 3-week arm, carboplatin at AUC 5 was given on day 1, and gemcitabine at 1,000 mg/m[^2^] was administered on days 1 and 8. The median number of chemotherapy cycles administered on-study was 4 and 6, respectively, for the two arms. The major toxicities were hematologic, and more adverse events occurred with the 3-week schedule. Grade 3/4 neutropenia occurred in 46% of patients on the 3-week schedule, compared with 27% of patients in the 4-week group. Grade 3/4 thrombocytopenia occurred in 50% and 38% of patients, respectively. Grade 3 nausea/vomiting was the major nonhematologic toxicity occurring in approximately 4% of the patients in the 3-week group and 19% of patients receiving the 4-week regimen. The incidence of grade 3/4 neutropenia was lower in the 4-week arm. However, there was no significant difference in the incidence of thrombocytopenia between the two arms. There were trends toward increased response rate in patients receiving the 3-week regimen (40% vs 23%), but with decreased median survival (7.3 vs 8.7 months) compared to the 4-week schedule. In a larger study, Obasaju et al recently reported the results of the surveillance trial of 473 patients with advanced NSCLC treated with either a 3- or 4-week regimen of carboplatin/gemcitabine.[31] The doses and schedule of treatment were similar to the study by Masters et al.[32] Both schedules of chemotherapy were well tolerated by the patients. The incidence of grade 3/4 thrombocytopenia was 8% and 14%, respectively, for the 4-week and 3-week arms. No clinically significant bleeding episodes were noted in either arms of the
study. Dose intensity of chemotherapy was similar for both arms. There were also no statistically significant differences in efficacy between the two schedules. There was 1 (2%) complete response and 20 (38%) partial responses, resulting in an overall response rate of 40% for patients receiving the 3-week schedule. Patients treated with the 4-week regimen had no complete responses and 11 (23%) partial responses for an overall response rate of 23%. Progression-free survival was 4.9 months with the 3-week regimen and 3.7 months with the 4-week regimen and median overall survival times were 7.3 months and 8.7 months, respectively. There were also no statistically significant differences in efficacy between the two schedules. The 3-week schedule of the carboplatin/gemcitabine combination has thus become the preferred regimen in the practice setting.

The combination of carboplatin and gemcitabine is effective for the treatment of patients with advanced NSCLC. The efficacy reported with this regimen in randomized trials is comparable to that reported for other commonly used combinations for the treatment of advanced NSCLC. The carboplatin/gemcitabine combination is associated with a relatively low incidence of nonhematologic toxicities, especially alopecia, whereas thrombocytopenia is dose limiting. The outcome for patients with advanced NSCLC has improved over the years with the availability of several novel combinations such as carboplatin/gemcitabine. It does appear, however, that an efficacy plateau has been reached with existing chemotherapy combinations. The role of "maintenance" therapy with single-agent gemcitabine is being evaluated in a randomized trial in patients who do not progress after four initial cycles of carboplatin/gemcitabine (Figure 2). A second ongoing randomized study is exploring the value of immediate docetaxel after carboplatin/gemcitabine vs the same treatment administered as true second-line therapy at progression (Figure 3). The efficacy of the carboplatin/gemcitabine regimen is also being evaluated in the earlier stages of NSCLC both in the neoadjuvant and adjuvant settings. Because of its overall tolerability and efficacy, the regimen of carboplatin/gemcitabine can be used as a backbone for evaluating novel molecularly targeted therapies.

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References:


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