New Investigative Regimens and Cytotoxic Agents in Thoracic Cancers: Gemcitabine and Pemetrexed

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Several new antimetabolites, administered alone or in combination, are changing the therapeutic landscape for thoracic cancer. Two-drug combinations involving these newer drugs are becoming the standard of care for non–small-cell lung cancer (NSCLC), largely due to improvements in survival rates, time to disease progression, and response rates as well as an improved safety profile. Gemcitabine (Gemzar) has elicited considerable interest in this disease, as a combination partner in chemotherapeutic regimens. Another promising agent is pemetrexed (Alimta), a folate-based inhibitor of thymidylate synthase. In preclinical development, pemetrexed both alone and in combination with other cytotoxic agents has exhibited activity across a broad range of tumor models, including NSCLC and mesothelioma. In clinical trials of patients with NSCLC, pemetrexed has been an effective, well-tolerated agent that can be used as monotherapy or in combination with other agents at full dose. In clinical trials of patients with mesothelioma, the combination of pemetrexed and cisplatin demonstrated a significant improvement in survival, response, and patient quality-of-life parameters. The principle toxicities of pemetrexed can be minimized by folate and vitamin B12 supplements.

In recent years, development of more effective and less toxic drugs has changed the therapeutic landscape for lung cancer. The urgent need for such improved treatment options is evidenced by the current US mortality trends. Among men, lung cancer has been the leading cause of cancer death for more than 50 years. In 2004, an estimated 93,110 men will be diagnosed with lung cancer and 91,930 will die of the disease. Among women, the mortality rate from lung cancer is lower, but is continuing to increase, even as breast cancer mortality is declining. An estimated 80,660 women will be diagnosed with lung cancer in 2004, of whom 68,510 will die.[1] If current trends continue, men and women will be equally at risk of developing and dying from the disease, and twice as many persons of each sex will die of the disease than from any other type of cancer. The current 5-year survival rate is approximately 16%. While that rate is higher than the 5-year survival rate of 5% reported in 1964, there is obviously considerable room for improvement, both in terms of earlier diagnosis and more effective, less toxic therapy of advanced disease. In this supplement, noted investigators in the field of lung cancer present articles with particular focus on gemcitabine (Gemzar) and pemetrexed (Alimta). First-line regimens in non–small-cell lung cancer (NSCLC), and the carboplatin (Paraplatin)/ gemcitabine and cisplatin/gemcitabine combinations in advanced NSCLC are discussed, as is the potential role of induction therapy in early-stage NSCLC. Other multimodality approaches such as chemoradiation are presented. The use of the promising antifolate pemetrexed is discussed in studies of pemetrexed administered as a single agent to patients with previously treated/untreated NSCLC. Another arena that is covered in this supplement is the role of pemetrexed either alone or in combination with cisplatin or carboplatin in the management of malignant mesothelioma. It is hoped that these data will benefit investigators in both basic and clinical research, as well as those involved in the design of future clinical trials. Gemcitabine Monotherapy When used as monotherapy, some of the newer agents offer at least equivalent survival and an improved safety profile over combinations of older chemotherapies used for treating NSCLC. For example, singleagent gemcitabine is as effective as many doublets, such as cisplatin plus either etoposide or vindesine (Eldesine), yet with much lower toxicity rates. In one randomized multinational multicenter study, a partial response was reported in 12 of 66 (18.2%) chemotherapy-naive patients treated with gemcitabine monotherapy, 1,000 mg/m² IV on days 1, 8, and 15 of a 28-day cycle. In comparison, partial response was achieved in 11 of 71 (15.5%) patients receiving combination cisplatin (100 mg/m² IV on day 1 of each 28-day cycle) plus etoposide (100 mg/m² on days 1, 2, and 3 after cisplatin).[2] There was no significant difference between the two treatment groups with respect to time to disease progression or survival. The combination therapy was markedly more toxic than gemcitabine monotherapy, with pronounced respective differences in neutropenic fever (11% vs 0%), nausea and vomiting (29% vs 11%), and alopecia (62% vs 11%).
second randomized study involved 169 NSCLC patients who were treated with either gemcitabine (1,000 mg/m²/day, 1, 8, and 15) or cisplatin (100 mg/m² on day 1, plus vindesine at 3 mg/m² on days 1 and 15), both every 4 weeks.[3,4] Response rates were similar in both the gemcitabine (20.2%) and combination therapy (20%) groups, with no important differences in objective response rate, time to progression, or median survival reported. Grade 3/4 toxicity was significantly higher in the cisplatin/vindesine group for leukopenia (P = .0003), neutropenia (P < .0001), nausea/vomiting (P = .0006), alopecia (P < .0001), and neurotoxicity (P = .04). Some severe pulmonary toxicity to gemcitabine was noted. These studies illustrate the current trend toward developing agents that can produce survival rates that are at least equivalent to those seen with combination therapy with less toxicity. The reduction in toxicity is particularly important among patients with NSCLC, who often have many comorbid diseases. Thus, newer drugs such as gemcitabine may provide a useful alternative strategy for patients for whom the main purpose of treatment is palliation.[5]

**Newer Two-Drug Combinations vs Single Agents**

Two-drug combinations involving the newer drugs (gemcitabine, docetaxel [Taxotere], paclitaxel, vinorelbine [Navelbine]) are replacing single-agent therapy as standard of care, largely due to improvements in survival rates, time to disease progression, and response rates, as supported by results of two recent randomized comparative studies. The first phase III study, which involved 522 chemotherapy-naive NSCLC patients, compared efficacy and safety of combination therapy with gemcitabine (1,000 mg/m² on days 1, 8, and 15) plus cisplatin (100 mg/m² on day 1 of a 28-day cycle) vs cisplatin alone (100 mg/m² IV on day 1 of a 28-day cycle).[6] Combination therapy demonstrated a significant improvement over cisplatin monotherapy with regard to response rate (30.4% vs 11.1%, P < .0001), median time to progressive disease (5.6 vs 3.7 months, P = .0013), and overall survival (9.1 vs 7.6 months, P = .0044). At 1 year, the estimated probability of survival was 39% for the gemcitabine/cisplatin arm compared with 28% for the cisplatin monotherapy arm. The 2-year survival rates were 15% and 8%, respectively. Toxicity was more pronounced in the combination arm than the monotherapy arm, including grade 4 neutropenia (35.3% vs 1.2%) and grade 4 thrombocytopenia (25.4% vs 0.8%). Similar benefits from combination therapy were observed in a second study, in which 415 patients were randomized to treatment with cisplatin at 100 mg/m² every 4 weeks, administered either as monotherapy or in combination with vinorelbine at 25 mg/m² weekly.[7] One-year survival was 20% for cisplatin alone and 36% for the combination arm. Two-year survival was 12% in the combination therapy group compared with 7% for cisplatin alone. There was a partial response rate of 12% vs a 26% response rate (2% complete response plus 24% partial response, P = .0002) in the combination arm. Significant advantages in progression-free survival (median 2 vs 4 months; P = .0001) and overall survival (median 6 vs 8 months; P = .0018). Grades 3 and 4 granulocytopenia was reported in 81% of the combination arm and 5% of the monotherapy arm. Other evidence supports use of the newer two-drug combinations rather than monotherapy with one of the new agents. In three recent clinical trials, addition of a second agent such as carboplatin or cisplatin to a monotherapy regimen of one of the new agents such as gemcitabine, docetaxel, or paclitaxel increased median survival by at least 2 months and increased 1-year survival by 4% to 12%.[8,9] Lilenbaum and the Cancer and Leukemia Group B (CALGB) reported a study (n = 99) comparing a regimen of paclitaxel alone vs paclitaxel plus carboplatin. Median survival was 6.7 months vs 8.8 months, respectively; 1-year survival rates were 33% vs 37%, respectively.[10] In a second comparative study (n = 307), Georgoulis and coworkers administered a regimen of docetaxel (100 mg/m² on day 1) plus cisplatin (80 mg/m² on day 2) was associated with longer median survival (10.1 vs 8.0 months) and higher 1-year survival rate (48% vs 42%) than cisplatin alone.[8] The most striking evidence in favor of combination therapy comes from a Swedish Lung Cancer Group study involving 322 patients with advanced NSCLC who were treated with either gemcitabine monotherapy at 1,250 mg/m² on days 1 and 8 every 21 days, or the same regimen of gemcitabine plus carboplatin, area under the concentration-time curve (AUC) 5 on day 1 every 21 days.[9] The objective response rate was 12% for the monotherapy group compared with 30% for the combination therapy group. Respective time to progression was 9.0 vs 11.0 months, and 1-year survival rates were 32% and 44%. **Doublet vs Doublet**

Results of a recent large (n = 1,155) study conducted by Schiller et al and the Eastern Cooperative Oncology Group (ECOG 1594) suggest that none of the newer two-drug combinations is clearly superior. Patients with advanced NSCLC were randomly assigned to a reference regimen of cisplatin and paclitaxel or to one of three experimental regimens: cisplatin and gemcitabine, cisplatin and docetaxel, or carboplatin and paclitaxel.[11] The overall response rate was 19%, with a median survival of 7.9 months. Survival rate was 33% at 1 year and 11% at 2 years. The response rate did not differ significantly between patients assigned to receive cisplatin and paclitaxel (17%) and those assigned to receive any of the three experimental regimens (cisplatin and gemcitabine, 22%;
cisplatin and docetaxel, 17%; and carboplatin and paclitaxel, 17%). Likewise, 1-year survival rates did not vary significantly between cisplatin and paclitaxel (31%) and the experimental regimens (cisplatin and gemcitabine, 36%; cisplatin and docetaxel, 31%; and carboplatin and paclitaxel, 34%). Kelly et al reported another randomized phase III trial (n = 408) that demonstrated equal efficacy between paclitaxel (225 mg/m², day 1 every 28 days) and carboplatin (AUC 6, day 1 every 21 days) compared with vinorelbine (25 mg/m²/wk) and cisplatin (100 mg/m²/day 1 every 28 days).[12] The response rate was 25% in the paclitaxel and carboplatin and 28% in the vinorelbine and cisplatin arm. Median survival was 8 months in both treatment arms, while 1-year survival rates were 38% and 36%, respectively. Significantly (P = .001) more patients in the vinorelbine and cisplatin arm discontinued therapy because of toxicity, particularly grade 3 and 4 leukopenia, neutropenia, and nausea and vomiting. 

**Carboplatin vs Cisplatin**

Several studies suggest that carboplatin compared with gemcitabine or with paclitaxel is as effective as cisplatin in combination with these agents. For example, two recent randomized trials suggest that gemcitabine plus carboplatin may be as effective as gemcitabine plus cisplatin for patients with advanced NSCLC. The first was a phase II study of 120 patients treated with either gemcitabine (1,200 mg/m² days 1 and 8) plus carboplatin (AUC 5 at day 2) or gemcitabine (1,200 mg/m² days 1 and 8) plus cisplatin (80 mg/m² day 2), with cycles repeated every 3 weeks.[13] The objective response rate was 41.9% for gemcitabine plus cisplatin and 31.0% for gemcitabine plus carboplatin (P = .29). Median survival was 10.4 months for gemcitabine plus cisplatin and 10.8 months for gemcitabine plus carboplatin. Overall toxicity was significantly more common in the gemcitabine plus cisplatin arm (P < .005). The second trial was a multicenter phase III trial by Zatloukal et al involving 176 patients.[14] Patients in both treatment arms were given gemcitabine (1,200 mg/m² on days 1 and 8) plus either cisplatin (80 mg/m2) or carboplatin (AUC 5). The overall response rates were 41% for the gemcitabine plus cisplatin arm and 29% for the gemcitabine plus carboplatin arm. Median survival was 8.8 and 8.0 months, respectively. Patients with at least one grade 3/4 toxicity, excluding nausea, vomiting or alopecia, were 44% in gemcitabine plus cisplatin arm and 54% in gemcitabine plus carboplatin group. The only significantly different toxicities were nausea and vomiting in the gemcitabine plus cisplatin group and thrombocytopenia in the gemcitabine plus carboplatin group. These studies suggest that the combination of gemcitabine plus carboplatin may be an acceptable alternative for patients with advanced NSCLC, especially when they are unable to receive cisplatin. The ECOG trial cited previously[11] is a good example of a trial showing equivalent efficacy for paclitaxel combined with either cisplatin or carboplatin. 

**Chemotherapy for Elderly Patients**

Age does not appear to be a significant independent prognostic factor for outcome in NSCLC, and elderly patients with good performance status can tolerate the same treatment as younger patients. In the Elderly Vinorelbine Study (ELVIS) of Gridelli et al involving 191 patients over 70, median survival was 28 weeks among those receiving vinorelbine (on days 1 and 8, every 21 days) compared with 21 weeks in those receiving best supportive care.[15] Respective 1-year survival rates were 32% and 14%. Moreover, patients who received vinorelbine fared better than controls on measures of lung cancer symptoms and pain and on social, cognitive, and physical functioning. Hematologic toxicity included grade 3/4 neutropenia in 10% of patients and grade 2/3 anemia in 16% of patients. The principal nonhematologic toxicities were constipation and fatigue. The question of whether elderly patients should receive one- or twodrug chemotherapy regimens has not been fully answered, although some recent trials suggest that two-drug combinations improve outcome. Frasci and colleagues conducted a randomized study of 240 patients with NSCLC between the ages of 71 and 85 years who received gemcitabine at 1,200 mg/m², plus vinorelbine at 30 mg/m² on days 1 and 8 every 3 weeks, or vinorelbine monotherapy.[16] Median survival was 28 weeks in the combination therapy group and 18 weeks in the vinorelbine monotherapy group. Respective projected 1-year survival was 30% and 13%. The rates of hematologic and nonhematologic toxicities were not significantly different in the
In the CALGB trial[10] comparing paclitaxel to the combination of paclitaxel/carboplatin, the combination was superior in all subsets including the elderly. In contrast, results of a phase II randomized study of suggest that monotherapy may be as active and tolerable as combination therapy in NSCLC patients over 70 years old. The 147 patients were randomly assigned to one of three regimens: single-agent gemcitabine at 1,200 mg/m² given on days 1 and 8; a combination of gemcitabine at 1,000 mg/m² and vinorelbine at 25 mg/m², both given on days 1 and 8 every 3 weeks; or vinorelbine monotherapy.[17] Median survival was 6.5 months for gemcitabine alone, 8.5 months for vinorelbine alone, and 7.4 months for combination therapy. Respective 1-year survival rates were 28%, 42%,
and 34%. With gemcitabine monotherapy, the principle toxicities were grade 4 thrombocytopenia and grade 2 hepatic toxicity in one patient each and grade 2 pulmonary toxicity in two patients. The combination regimen was associated with grade 5 neutropenia and thrombocytopenia in one patient each, grade 3 anemia necessitating transfusion in two patients, and grade 4 fever in two patients. In addition, four patients with severe cardiac comorbidities experienced grade 3 heart toxicity.

**Performance Status and Choice of Regimen**

Performance status (PS) has been established as an independent prognostic variable, as patients with PS 2 have a significantly lower rate of survival than those with a PS of 0 or 1.[11] Some evidence suggests that cisplatin-containing combinations, including those with paclitaxel, gemcitabine, or docetaxel, are too toxic for PS 2 patients. In ECOG 1594, for example, which involved 64 PS 2 patients with advanced NSCLC, Sweeney et al reported that the proportion of patients who developed grades 3, 4, or 5 toxicity ranged from 55% to 88% during therapy with four different regimens: paclitaxel (135 mg/m\(^2\)) over 24 hours with cisplatin (75 mg/m\(^2\)) on a 21-day cycle; cisplatin (100 mg/m\(^2\)) with gemcitabine (1,000 mg/m\(^2\)) on days 1, 8, and 15 on a 28-day cycle; cisplatin (75 mg/m\(^2\)) with docetaxel (75 mg/ m\(^2\)) on a 21-day cycle; and paclitaxel (225 mg/m\(^2\)) over 3 hours with carboplatin (AUC 6).[18] Nonhematologic grade 3/4 toxicities occurred significantly less often in the paclitaxel and carboplatin arm (P = .0032). (Note that the cisplatin dose of 100 mg/m\(^2\) in the cisplatin/gemcitabine arm was higher than what is normally used in actual practice, because cisplatin doses above 80 mg/m\(^2\) only add incrementally more toxicity without efficacy.) The overall response rate was 14%, and the overall median survival was 4.1 months. None of the four regimens tested demonstrated any survival advantage. A subsequent study by Langer et al compared 98 PS 2 patients who were randomized to receive paclitaxel (200 mg/m\(^2\)) plus carboplatin (AUC 6 every 3 weeks) or gemcitabine (1,000 mg/m\(^2\) on days 1 and 8) plus cisplatin (50 mg/m\(^2\) day 1 every 3 weeks). For the gemcitabine/cisplatin arm, the overall response rate was 21% and median survival was 6.8 months. Respective findings for the paclitaxel/carboplatin arm were 10% and 6.1 months.[19] In the CALGB trial,[10] the combination of paclitaxel/carboplatin was superior to paclitaxel alone in the PS 2 subset.

**Second-Line Chemotherapeutic Regimens**

For second-line therapy, some new agents such as docetaxel have been shown to provide clinically meaningful survival benefit to patients with advanced NSCLC whose disease has relapsed or progressed after platinum-based chemotherapy. Fossella et al conducted a randomized study of 373 patients with advanced NSCLC who had previously failed platinum-containing chemotherapy.[20] Survival was determined for regimens of docetaxel, in dosages of either 75 or 100 mg/m\(^2\), compared with a control regimen of vinorelbine or ifosfamide (Ifex). Overall response rates for the docetaxel 75 and 100 mg/m\(^2\) groups and the control group were 6.7%, 10.8%, and 0.8%, respectively (P = .036 and P = .001). Median survival was 7.0, 6.5, and 6.0 months. One-year survival was 37%, 30%, and 19%. A second study compared outcome in 103 NSCLC patients who received either docetaxel at 75 mg/m\(^2\), or best standard care after failing platinum-based chemotherapy.[21] Overall response rates were 6% and 0%, and median survival was 7.5 and 4.6 months (P = .01), respectively. At 1 year, the survival rates were 37% and 12% (P = .003). Results of these studies support standard use of docetaxel, 75 mg/m\(^2\) IV every 3 weeks, for standard second-line therapy. **Pemetrexed**

Pemetrexed is a novel cytotoxic agent that was designed as a thymidylate synthase inhibitor similar to methotrexate, raltitrexed, and lomtrexol (Figure 1).[22] It inhibits multiple enzymes in the DNA synthesis pathway, including thymidylate synthase, glycaminide ribonucleotide formyltransferase, and dihydrofolate reductase (Figure 2).[23] Hence, the original name was multitargeted antifolate. Most lung cancers overexpress thymidylate synthase and a variety of genes involved in cell cycle regulation.[24] **Preclinical Studies**

In preclinical development, pemetrexed both alone and in combination with other antitumor agents has exhibited antitumor activity across a broad range of tumor models, including some that are generally considered chemoresistant. In vitro, pemetrexed has been shown to inhibit growth of a large panel of human cancer cell lines, including lung cancer and mesothelioma, as well as colorectal cancer, renal cell carcinoma, hepatocellular carcinoma, and pancreatic cancer.[25,26] In vivo studies of human NSCLC xenografts in athymic nude mice demonstrated that pemetrexed appears to be especially effective in combination therapies. Addition of pemetrexed to fluorouracil, gemcitabine, cisplatin, vinorelbine, carboplatin, oxaliplatin (Eloxatin), doxorubicin, and paclitaxel produced additive or synergistic growth inhibition. Pemetrexed appeared to be especially effective in combination with fluorouracil or an antitumor platinum complex. **Phase I Trials**

The phase I trials of single-agent pemetrexed have used a daily * 5 schedule every 3 weeks, weekly for 4 weeks every 6 weeks, and once every 3 weeks. in patients with a variety of solid tumors (Table 1).[27-29] The best tolerability profile occurred in the study of 37 patients by Rinaldi and coworkers who administered dosages ranging from 50 to 700 mg/m\(^2\) every 3 weeks, and reported that four
patients achieved a partial response and six a minor response. The maximum tolerated dose was 600 mg/m²; this was the dose selected for further study, although subsequent evidence of hematologic and cutaneous toxicity prompted a starting dose reduction to 500 mg/m².[29] In all phase I trials, neutropenia was the major dose-limiting effect, regardless of regimen. Nonhematologic toxicities included anorexia, mild nausea, diarrhea, mucositis, rash, and reversible elevations of hepatic enzymes.

Table 1
Overview of Phase I Trials of Pemetrexed for Patients With Various Solid Tumors

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Dose/Schedule</th>
<th>MTD/Schedule</th>
<th>Dose-Limiting Effects</th>
<th>Responses*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rinaldi[27]</td>
<td>25</td>
<td>10-40 mg/m² weekly × 4 q6wk</td>
<td>40 mg/m² weekly × 4 q6wk</td>
<td>Neutropenia</td>
<td>2</td>
</tr>
<tr>
<td>Rinaldi[28]</td>
<td>37</td>
<td>50-700 mg/m² q3wk</td>
<td>700 mg/m² q3wk</td>
<td>Neutropenia</td>
<td>6 4</td>
</tr>
<tr>
<td>McDonald[29]</td>
<td>38</td>
<td>0.2-5.2 mg/m² daily ×5 q3wk</td>
<td>4.0 mg/m² daily ×5 q3wk</td>
<td>Neutropenia</td>
<td>2</td>
</tr>
</tbody>
</table>

*Column entries denote number of patients.
MTD = maximum tolerated dose.

Folate and Vitamin B₁₂ Supplementation

Plasma homocysteine levels, which are inversely related to folate levels, and vitamin B₁₂ levels appear to be highly predictive of pemetrexed toxicity. Patients with low B₁₂ and folate pools appear to be at greater risk of severe pemetrexed-related toxicity, such as neutropenia, thrombocytopenia, mucositis and febrile neutropenia, which in turn, have been significantly correlated with drug-related death.[31] Conversely, administration of basic dietary supplements including 350 to 1,000 μg/d of oral folate and 1,000 μg B₁₂ intramuscularly every 9 weeks markedly reduces drug-related toxicity (Table 2). Dietary supplements have proven to be indicated for patients who receive pemetrexed, and are recommended for patients receiving pemetrexed therapy.[31,32]
Mesothelioma, a highly aggressive tumor arising from the surface serosal cells of the pleura, has been even more discouraging a topic for therapeutic intervention than NSCLC. There have been no approved cytotoxic therapies for mesothelioma until the recent US Food and Drug Administration (FDA) approval of pemetrexed in combination with cisplatin, and there was little evidence that any chemotherapy regimen given as part of multimodality treatment, including radiotherapy and surgery, can improve survival.[33] Surgery has successfully limited spread of disease in only a small minority of select cases. Radiotherapy to the entire chest is dangerous and is used only for palliation of localized symptomatic disease. Interest in mesothelioma has increased recently, as the prevalence is expected to peak over the next 20 years.[33] Some antimetabolites, such as pemetrexed administered alone or in combination with cisplatin, have shown promise in phase II study data.[34] In addition, pemetrexed in combination with cisplatin has currently been evaluated by Vogelzang et al in a phase III trial with survival as the primary end point.[35] The trial demonstrated statistically significant superiority of the pemetrexed/cisplatin regimen in comparison with cisplatin alone in survival, response, and patient quality of life. In February 2004, the FDA approved this combination as first-line therapy for mesothelioma. Conclusion Clearly, there is an urgent need for improved therapies to treat NSCLC and mesothelioma.[36,37] As the following articles will demonstrate, one of the most promising agents is the multitargeted antifolate pemetrexed. Results of preliminary studies suggest that pemetrexed is a well-tolerated single agent that can be combined with multiple other agents at or near their single-agent doses.

**Disclosures:**
Dr. Bunn has received research grant support and honoraria and has served as a member of the speakers’ bureau for Eli Lilly and Company, Bristol-Myers Squibb, Aventis, and GlaxoSmithKline.

**References:**
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