Chemoradiation in NSCLC: Focus on the Role of Gemcitabine

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By Hak Choy, MD [2]

Research to identify the optimal drugs for use in chemoradiotherapy has led to the development of the potent radiosensitizing agent gemcitabine (Gemzar), which has exhibited excellent activity in non-small-cell cancer. When used in sequential chemoradiotherapy regimens, gemcitabine has been associated with response rates of 57% to 68%. A full dose of gemcitabine (1,000 mg/m²) can be safely used as induction therapy, and there is no definitive indication of enhancement of radiotoxicity. In addition, results from phase I/II trials support the efficacy of concurrent gemcitabine/radiation therapy in improving overall response rates and overall survival. Rates of 68%, 37%, and 28%, respectively, for 1-, 2-, and 3-year survival have been reported for gemcitabine/cisplatin chemotherapy administered concurrently with radiotherapy. Although the optimal dose has yet to be determined, a weekly dose of 300 mg/m² appears to be effective with an acceptable toxicity level. Additional clinical trials are warranted to assess the longterm efficacy and safety of gemcitabine in combination with other chemotherapeutic agents and radiation therapy for treatment of non-small cell lung cancer.

The discovery that chemotherapy and radiation therapy separately improve response rates and survival in patients with non-small-cell lung cancer (NSCLC) has spurred considerable interest in determining the optimal use of these treatment modalities. Initial research demonstrated that sequential chemoradiation therapy consistently improves survival in locally advanced NSCLC compared with either radiation therapy or chemotherapy alone. Chemoradiation: Sequential vs Concurrent In a series of clinical trials, the 2-year overall survival ranged between 19% to 25% in those receiving sequential chemoradiation therapy compared with 13% to 17% in patients treated with radiotherapy alone.[1-4] Similarly, phase II studies conducted in Japan showed a 2-year survival rate of 36% for patients receiving chemoradiation therapy compared with 9% for chemotherapy alone; by 3 years, the respective survival rates were 30% and 3%.[5] There is no role for chemotherapy alone in stage III disease. Subsequently, six clinical trials conducted in Europe, Asia, and the United States addressed the key issue of determining the optimal sequence of chemotherapy and radiation therapy.[ 6-10] Regardless of what drug was given or where the study was done, results consistently demonstrated that concurrent chemoradiotherapy provided longer mean survival than sequential chemoradiotherapy. The average median survival was about 14 months for sequential chemoradiotherapy and approximately 17 months for concurrent radiochemotherapy (P < .05) (Figure 1; unpublished data). The survival benefits have been maintained for as long as 5 years. In one long-term study, a chemotherapy regimen of cisplatin (80 mg/m² on days 1 and 29), vindesine (3 mg/m² on days 1, 8, 29, and 36), and mitomycin (8 mg/m² on days 1 and 29) was administered either before or at institution of radiotherapy (28 Gy) in 323 patients with NSCLC. The 5-year overall survival rate was 9% for patients receiving sequential chemoradiation therapy vs 19% for concurrent chemoradiation therapy.[6]
Similarly, in a study involving 610 patients with NSCLC who were treated with either cisplatin (100 mg/m² on days 1 and 29) plus vinblastine (5 mg/m² on days 1, 8, 29, and 36) or cisplatin (50 mg/m² on days 1, 8, 29, and 36) plus oral etoposide (50 mg bid for 10 weeks) with radiation (60 to 69.6 Gy), the 5-year survival rates were 12% and 21% for sequential and concurrent chemoradiation therapy, respectively.[11] These findings strongly suggest that synergy between treatment modalities improves locoregional control and survival. The disadvantage is that enhanced toxicity may restrict the ability to delivery full doses of both modalities. For that reason, concurrent chemoradiotherapy may be indicated for patients whose performance status is 0 or 1.

**Gemcitabine and Radiation Therapy**

Research to identify the optimal drugs for use in concurrent chemoradiotherapy has lead to the development of a number of new agents, such as paclitaxel, irinotecan (Camptosar), docetaxel (Taxotere), and vinorelbine (Navelbine). Among the more promising new options is the novel deoxycytidine analog gemcitabine (Gemzar), which has demonstrated excellent single-agent activity in NSCLC.[12] In preclinical studies, gemcitabine has exhibited cell phase specificity, primarily by killing the radioresistant cells undergoing DNA synthesis (S-phase cells) and also by blocking the progression of cells through the G1/S-phase boundary.[13-17] The cytotoxic effects of gemcitabine are attributed to the active diphosphate and triphosphate nucleosides. Diphosphate gemcitabine facilitates incorporation of triphosphate gemcitabine into DNA, which ultimately inhibits DNA synthesis and induces apoptosis. These cytotoxic effects render gemcitabine a potent radiosensitizer for NSCLC.[12] The sensitizer enhancement ratio is ≥ 1.5.[13,14] Duration of sensitization after exposure exceeds 76 hours.[15,16] Sensitization occurs at subcytotoxic doses and is induced more...
rapidly with higher doses. **Gemcitabine in Sequential Therapy** Gemcitabine is indicated in combination with cisplatin as first-line therapy for locally advanced (stage IIIA or IIIB) or metastatic (stage IV) NSCLC.[17] When administered in dosages between 1,000 and 1,750 mg/m$^2$, gemcitabine has been associated with response rates ranging from 57% to 68% (Table 1).[18-24] A major advantage of gemcitabine is its low toxicity when administered sequentially as monotherapy or combined with cisplatin, followed by radiation. (It may be administered in patients with low performance status of 1 or 2.) However, gemcitabine should be used with caution after radiotherapy, because it has been associated with radiation recall syndrome, a rare but serious phenomenon.[25] A full dose of gemcitabine (1,000 mg/m$^2$) can be used safely with cisplatin as induction therapy followed by radiation. In a potentially curative setting, an interval of 1 to 4 weeks is recommended between gemcitabine and radiotherapy to minimize the risk of radiation recall syndrome. In a palliative setting, however, when radiotherapy is used to treat bone metastases, the interval between chemotherapy and radiation therapy can be reduced if necessary.

### Table 1

<table>
<thead>
<tr>
<th>Author</th>
<th>II</th>
<th>Chemotherapy Schedule</th>
<th>Radiotherapy</th>
<th>Efficacy</th>
<th>Grade 3/4 Toxicity</th>
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<tbody>
<tr>
<td>Cisplatin</td>
<td>15</td>
<td>G1,200 + C70</td>
<td>42-70 Gy</td>
<td>RR 37%</td>
<td>No grade 3/4 toxic</td>
</tr>
<tr>
<td>Ili[16]</td>
<td>20</td>
<td>G1,100 + C100</td>
<td>60 Gy</td>
<td>RR 65%</td>
<td>OS 13 mo</td>
</tr>
<tr>
<td>Vincoli[21]</td>
<td>20</td>
<td>G1,600 + C300</td>
<td>61.6 HF</td>
<td>RR 90%</td>
<td>OS 13.6 mo</td>
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<tr>
<td>Van Zandwijk[20]</td>
<td>18/2</td>
<td>G1,100 + C100 x 3</td>
<td>55 Gy</td>
<td>RR 90%</td>
<td>OS 13.6 mo</td>
</tr>
<tr>
<td>Migliorini[24]</td>
<td>20</td>
<td>G1,200 + C70</td>
<td>54-65 Gy</td>
<td>RR 57%</td>
<td>OS 14.5 mo</td>
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<tr>
<td>Crino[23]</td>
<td>70 h20</td>
<td>G1,200 + C100 x 4</td>
<td>54 Gy</td>
<td>RR 65%</td>
<td>HF</td>
</tr>
<tr>
<td>De Braud[18]</td>
<td>30</td>
<td>G1,200 + C100 x 4</td>
<td>54 Gy</td>
<td>RR 65%</td>
<td>No grade 3/4 toxic</td>
</tr>
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</table>

**Gemcitabine and Concurrent Radiation Therapy Phase I/II Trials**

The activity of concurrent gemcitabine and radiation therapy in NSCLC was initially demonstrated in a multiinstitutional phase II pilot study conducted from October 1994 through August 1995.[26] The treatment regimen included gemcitabine at 1,000 mg/m$^2$/wk for 6 weeks, given together with radiation administered as a 2-Gy fraction 5 days/wk up to a maximum dose of 60 Gy.[26] Seven of the eight patients had a > 50% reduction in the primary tumor, and four of five patients experienced a response in the nodes. The excellent activity of this regimen, however, was accompanied by serious toxicity. There were three treatment-related deaths, two due to pulmonary toxicity and one resulting from hemorrhage due to radiation necrosis. Three patients experienced pneumonitis or severe esophagitis, and another two patients experienced serious radiation-induced side effects. Two factors were believed to be primarily responsible for this toxicity. First was the large starting dose of gemcitabine, which had been chosen before results of phase I dose-escalation studies had been completed. Second was the large radiation treatment volume, which encompassed approximately 5,000 cm$^3$ for the initial volume and 2,000 cm$^3$ for the booster field. Those volumes are approximately twice the volumes that are recommended in the United States (personal communication, A. Turrisi A, H. Choy, 2003). Subsequent phase I studies have demonstrated that gemcitabine, in doses ranging from 100 to 600 mg/m$^2$/wk, are well tolerated during radiation therapy.[27-30] The risk of serious toxicity increased substantially with the dose, and the maximum tolerated dose ranged from 190 to 350 mg/m$^2$/wk. A recent randomized phase II study supports administration of gemcitabine with cisplatin during radiation therapy for NSCLC.[31] Chemotherapy,
consisting of cisplatin combined with gemcitabine, paclitaxel, or vinorelbine, was administered in two cycles of induction chemotherapy followed by two additional cycles of the same drugs with concomitant radiotherapy. All 175 patients received four cycles of cisplatin at 80 mg/m^2 on days 1, 22, 43, and 65. Dosage schedules for the three different treatment arms were as follows: gemcitabine at 1,250 mg/m^2 on days 1, 8, 22, and 29, and 600 mg/m^2 on days 43, 50, 64, and 71; paclitaxel at 225 mg/m^2 for 3 hours on days 1 and 22, and 135 mg/m^2 on days 43 and 64; and vinorelbine at 25 mg/m^2 on days 1, 8, 15, 22, and 29, and 15 mg/m^2 on days 43, 50, 64, and 71. Radiotherapy was instituted on day 43 at 2 Gy/d (total dose, 66 Gy).

Response rates after completion of radiotherapy were 74%, 67%, and 73%, respectively, for the gemcitabine, paclitaxel, and vinorelbine arms. Median survival for all patients was 17 months. Median progression-free survival was 8.4 months with gemcitabine/ cisplatin, 9.1 months with paclitaxel/ cisplatin, and 11.5 months with vinorelbine/cisplatin. Rates were 68%, 37%, and 28% for 1-, 2-, and 3- year survival, respectively, for the gemcitabine arm; 62%, 29%, and 19% for the paclitaxel arm; and 65%, 40%, and 23% for the vinorelbine arm (Figure 2). The study was too small to show statistical significance in survival rates between treatment groups, although the numerically higher 3-year survival rate for the gemcitabine/ cisplatin arm appears to be encouraging. Toxicities during induction chemotherapy consisted primarily of grade 3 or 4 granulocytopenia. Grade 3 or 4 toxicities during concomitant chemoradiotherapy most frequently involved thrombocytopenia, granulocytopenia, and esophagitis. Of the group receiving the vinorelbine/cisplatin combination, 10 patients experienced grade 4 lung toxicity, and 1 patient died as a result of treatment-related respiratory failure.

**Dose-Escalation Trial**

The optimal dosage of gemcitabine during radiation therapy for NSCLC is being assessed in an ongoing "Ping-Pong" trial (RTOG 0017), in which patients are recruited into treatment sequences involving escalating dosages of either gemcitabine plus carboplatin or gemcitabine plus paclitaxel (unpublished data). However, as of publication, sequence B- the "Pong" portion of the trial-has closed due to safety concerns about toxicities. The original design was as follows. In sequence A, there are five dosages of gemcitabine used in the six gemcitabine/carboplatin treatment arms: 300 mg/m^2/wk (including one monotherapy and one combination therapy arm), 450, 600, 750, and 900 mg/m^2/wk. Carboplatin will be given at an area under the concentration- time curve (AUC) of 2 in five treatment arms, but not used in the sixth. Sequence B was designed to include six treatment arms involving gemcitabine and paclitaxel, respectively, in dosages as follows: 300/30, 450/30, 450/40,
600/40, 600/50, and 750/50 mg/m²/wk. All arms would be followed by two cycles of consolidated chemotherapy, gemcitabine at 1,000 mg/m² weekly 2 out of 3, and carboplatin at AUC 5.5. Patients will be recruited first into the lowest-dose arm of sequence A (300 mg/m²/wk gemcitabine monotherapy). After recruitment is completed in the first arm, toxicity will be assessed, while patients are being entered into the lowest dose arm of sequence B (gemcitabine at 300 mg/m²/wk plus paclitaxel 30 mg/m²/wk). While the toxicity of that regimen is being evaluated, patients are recruited into the second lowest dose arm in sequence A (gemcitabine at 300 mg/m²/wk plus carboplatin AUC 2). Recruitment will continue at escalating dosage levels until toxicity becomes unacceptable. Dose escalation continues as long as ≤ two of six patients experience dose-limiting toxicity. The estimated accrual is 36 patients, six per treatment arm. Preliminary toxicity data have been derived from the first 24 patients, seven each in the first three arms. Grade 3/4 hematologic toxicity occurred in four of seven patients in arm 1 (gemcitabine at 300 mg/m²/wk monotherapy), five of seven patients in arm 2 (gemcitabine at 300 mg/m²/wk plus paclitaxel at 30 mg/m²/wk), and four of seven patients in arm 3 (gemcitabine at 300 mg/m²/wk plus carboplatin at AUC 2). Pulmonary toxicity was noted only in two patients in arm 2. Since three patients in arm 2 had doselimiting toxicities, researchers concluded that the combination of gemcitabine plus paclitaxel is too toxic, and recruitment of patients to receive this combination has been discontinued. By contrast, recruitment into treatment arms involving escalating dosages of gemcitabine plus carboplatin is expected to continue. Conclusion The efficacy of gemcitabine as a radiosensitizer is strongly supported by accumulating clinical data. When administered together with radiation therapy, gemcitabine is associated with favorable overall survival and response rates, and may be used in patients with a low performance status. Although the safe weekly dose of gemcitabine has yet to be determined, it appears to be at least 300 mg/m². An ongoing clinical trial may soon establish the maximum tolerated dose of gemcitabine to be used during radiation therapy. Toxicity may be minimized by using modern technology such as three-dimensional conformal radiotherapy. Additional clinical trials are needed to assess the long-term efficacy and safety of gemcitabine administration during radiotherapy.

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