Gemcitabine for the Treatment of Non-Small-Cell Lung Cancer

By David H. Johnson, MD [2]

Platinum-based chemotherapy regimens have been the mainstay of treatment for non-small-cell lung cancer because they improve survival. Although there is no standard platinum-based regimen, combination regimens with

**Introduction**

During the past 3 decades, extensive experience has been gained in the treatment of patients with stage III or IV lung cancer. A total of 42 phase III trials were initiated by the National Cancer Institute between 1973 and 1994 and included 9,161 patients. A meta-analysis of these North American trials included 32 of the 42 trials, for a total of 5,820 patients, and divided the trials into two time frames: 1973 to 1983 and 1984 to 1994.[1] While the percentage of women enrolled in clinical trials of lung cancer treatment was unchanged between the two time frames (27% and 28%), there was a significant increase in the median number of patients per treatment arm (77 vs 130; *P* < .001). Five trials found a median prolongation of survival of 2 months (range: 0.7 to 2.7 months). In both time frames, median survival time was greater with cisplatin (Platinol)-based regimens: 1973 to 1983, 5.7 vs 4.4 months (*P* < .001); 1984 to 1994, 6.0 vs 4.4 months (*P* < .37). Many of the trials were underpowered to show a significant improvement in median survival time. For example, a study with 130 patients per treatment arm has 70% power to detect an improvement in median survival time from 6 to 8 months.

Based on North American and worldwide experience, platinum-based regimens have been the mainstay of chemotherapy regimens for non-small-cell lung cancer for several decades. These regimens significantly reduce the risk of death, increase median survival, and improve 1-year survival.[1,2] There is no standard platinum-based regimen, but combination regimens with newer agents, such as gemcitabine [Gemzar], paclitaxel [Taxol], and vinorelbine [Navelbine], are superior to platinum alone or in combination with older agents such as etoposide and vindesine [Eldisine].[3] The focus of this article is the experience with platinum-based regimens that include gemcitabine, a deoxycytidine analog. Four phase III clinical trials of gemcitabine for the treatment of non-small-cell lung cancer have been published in full.[4-7] These trials and the recently reported Eastern Cooperative Oncology Group (ECOG) E1594 trial, which demonstrated the activity of gemcitabine, are discussed.

**Gemcitabine/Cisplatin**

Approval by the US Food and Drug Administration (FDA) of gemcitabine for use in non-small-cell lung cancer was based on a study that compared cisplatin/gemcitabine with cisplatin [Platinol] alone in approximately 260 patients per treatment arm.[4] The study randomized 522 assessable patients (mean age: 62 to 63 years) who had not received prior treatment for non-small-cell lung cancer to either cisplatin/gemcitabine or cisplatin alone administered on a 28-day schedule. The treatment groups were well balanced with respect to disease severity: 18 of 68 patients in the cisplatin/gemcitabine group and 17 of 61 in the cisplatin group had stage IIIA/IIIB disease, respectively, and the numbers of patients with stage IV disease were 174 vs 184 (cisplatin/gemcitabine vs cisplatin).

Grades 3/4 hematologic toxicities occurred more frequently in the gemcitabine combination treatment group than in the cisplatin-alone group (25.4% vs 0.8%).[4] Neutropenia and thrombocytopenia were common: 57% and 50%, respectively, in the cisplatin/gemcitabine group vs 4.5% and 3.6% in the cisplatin group. Anemia (low hematocrit) was noted in 25% of cisplatin/gemcitabine-treated patients and 6.5% of cisplatin-treated patients, while the incidence of febrile neutropenia was modest (4.6% and 0.8%). The incidence of nonhematologic toxicities...
reflected primarily the cisplatin component and generally were comparable for the two treatment groups. Nausea and vomiting were reported by 27% and 23% of patients receiving cisplatin/gemcitabine and 21% and 19% of those receiving cisplatin, and renal toxicity occurred in approximately 5% and 2% of these patients, respectively. Neurotoxicity was more common with cisplatin/gemcitabine: 17.5% vs 8.6% for cisplatin alone.

Response parameters all favored the cisplatin/gemcitabine arm (Table 1).[4] The overall response rate for cisplatin/gemcitabine was 30.4% vs 11.1% for cisplatin (P < .0001), and the median survival time was 9.1 vs 7.6 months, respectively (P = .004). One-year survival was also notably higher for cisplatin/gemcitabine-treated patients, 39% vs 28%. The time to progressive disease and the survival time significantly favored the cisplatin/gemcitabine combination regimen over treatment with cisplatin alone (P = .0013 and P = .004, respectively) (Figure 1).

### Gemcitabine/Cisplatin vs Cisplatin/Etoposide

A second phase III, randomized trial was conducted in a similar patient population (no prior treatment, stage IIIB or IV non-small-cell lung cancer).[5] This Spanish trial of 135 patients compared gemcitabine/cisplatin administered in a 21-day schedule with cisplatin/etoposide in an every 28-day schedule. The primary end point was overall response rate. Approximately 50% of patients (mean age: 58 to 59 years) in each group had stage IV disease.

Overall, toxicity was comparable for the two treatment regimens.[5] The incidence of neutropenia was higher in etoposide- than in gemcitabine-treated patients (76% vs 64%), which corresponds to other studies of etoposide-containing regimens, while the incidence of grade 3/4 thrombocytopenia was greater with gemcitabine (56% vs 13%). Seven gemcitabine-treated patients and 12 etoposide-treated patients developed febrile neutropenia. The incidence of nausea and vomiting was similar in both treatment groups (39% vs 26%), while grade 3 alopecia was far more common with etoposide (13% vs 51%).

Response to treatment was greater with gemcitabine than with etoposide (Table 1).[5] The overall response rates were 40.6% and 21.9% (P = .02), and the time to progression was 6.9 vs 4.3 months (P = .01) for gemcitabine vs etoposide. A trend toward increased median survival time and 1-year survival of 8.7 months and 32% was seen for gemcitabine, compared with 7.2 months and 26% for etoposide. The progression-free survival curve significantly favored gemcitabine, and the survival curve favored gemcitabine, although not significantly. The authors concluded that compared with etoposide/cisplatin, the gemcitabine-containing regimen provided a significantly higher response rate and a delay in disease progression, without impairing quality of life.

### Gemcitabine/Cisplatin vs Cisplatin Triplet

An Italian phase III trial, which included 307 patients with stage IIIB or IV non-small-cell lung cancer who had not received previous treatment, randomly assigned patients to either gemcitabine plus cisplatin or mitomycin (Mutamycin) plus ifosfamide (Ifex) plus cisplatin. Both regimens were administered on a 28-day schedule.[6] The majority of patients (mean age: 60 to 62 years) in each treatment group had stage IV disease (123, gemcitabine; 120, triplet regimen).

The incidence of grade 3/4 hematologic toxicities was similar in both groups, although a higher proportion of patients in the gemcitabine group experienced thrombocytopenia (64% vs 28%; P < .001).[6] Neutropenia occurred in 40% and 33% of patients receiving the gemcitabine and triplet regimen, respectively; the occurrence of febrile neutropenia was rare (1% vs 0%). Nonhematologic toxicities occurred with similar incidence in both treatment groups, except alopecia which had a threefold higher incidence in the triplet regimen group (12% vs 39%; P < .001).

The overall response rate to the gemcitabine regimen (59%) was higher than with the triplet regimen (40%; Table 1).[6] The time to progression was similar in both groups (5.0 vs 4.8 mo) as was the 1-year survival (33% vs 34%). There were no differences between the two regimens in the progression-free survival and survival curves. The results of this study are noteworthy in that, in previous studies, the mitomycin, ifosfamide, and cisplatin regimen was shown to be superior to
supportive care and doublet regimens. The study provides further support of the benefit of gemcitabine/cisplatin in the treatment of non-small-cell lung cancer.

**Gemcitabine, Cisplatin, Vinorelbine**

An ongoing, phase III Italian study, though underpowered, has provided some interesting preliminary results (Table 1). The study is comparing the triplet regimen of gemcitabine, cisplatin, and vinorelbine with gemcitabine/cisplatin; a third treatment arm, cisplatin/vinorelbine, was discontinued due to a markedly higher incidence of neutropenia. Sixty patients (mean age: 60 to 62 years) with stage IIIIB or IV non-small-cell lung cancer who had not been previously treated were randomized to each treatment. A higher proportion of patients had stage IV disease (57% to 60%), and the majority of patients had a performance status of 1.

Occurrences of grade 3/4 hematologic toxicities were comparable for the three treatment groups with the exception of neutropenia. Treatment regimens containing gemcitabine were associated with a 40% to 45% incidence of neutropenia, whereas the cisplatin/vinorelbine regimen was associated with a 75% incidence. Thrombocytopenia did not differ markedly among groups: 30% for gemcitabine/cisplatin, 17% for gemcitabine/cisplatin/vinorelbine, and 20% for cisplatin/vinorelbine. Fatigue was common with all three regimens (10%, 14%, 15%).

Response to the gemcitabine-containing regimens was superior to the cisplatin/vinorelbine regimen: 30% with gemcitabine doublet (95% confidence interval [CI] = 19%-43%) and 47% with gemcitabine triplet regimens (95% CI = 34% to 60%) vs 25% with cisplatin/vinorelbine (95% CI = 15% to 38%) (see Table 1) as was the 1-year survival rate (40% and 45% vs 34%). Median survival time was 42 and 51 weeks with the gemcitabine regimens compared with 35 weeks for the cisplatin/vinorelbine regimen. In patients with stage IV non-small-cell lung cancer, the median survival time also favored the gemcitabine regimens: 34 and 47 weeks vs 27 weeks for the cisplatin/vinorelbine regimen. Both the median survival time and the 1-year survival rate for the gemcitabine/cisplatin regimen observed in this study are comparable to those achieved in the ECOG E1594 clinical study discussed below.

**ECOG E1594 Phase III Study**

The ECOG E1594 study evaluated four doublet regimens commonly used for the treatment of non-small-cell lung cancer. Patients were stratified by stage of disease (IIIB vs IV), performance status 0 to 1 vs 2, weight loss (< 5% vs ≥ 5%), and whether they had metastases to the central nervous system. They were then randomized to one of four treatments: cisplatin/paclitaxel (the reference treatment arm), cisplatin/gemcitabine, cisplatin/docetaxel (Taxotere), or carboplatin (Paraplatin)/paclitaxel (Figure 2). At an interim analysis after approximately 100 patients with a performance status of 2 had been treated, enrollment of performance status 2 patients, and hence stratification by performance status, was suspended due to excessive toxicity with all four treatment regimens.

Nearly 1,200 patients (approximately 300 per treatment arm) were enrolled in the E1594 study, and the treatment groups were comparable with respect to prognostic factors. The mean age of patients ranged from 61.6 to 63.9 years with a slight preponderance of males (61% to 64%), and the majority of patients had stage IV non-small-cell lung cancer (84% to 87%). Patients with stage IIIB disease had malignant pleural effusions. Approximately 12% to 14% of patients in each group had metastases to the central nervous system that were controlled by radiation therapy and/or surgery. The median number of weeks of treatment in all four arms was 12.

Overall, the response to treatment and survival were comparable among treatment groups (Table 2). The response rate in the gemcitabine arm (20.8%) was equivalent to that in the paclitaxel reference arm (21.2%), while the response rates were somewhat lower, but not statistically different, in the docetaxel (17.4%) and carboplatin (15.5%) arms. Response rates in this study are somewhat lower than in other studies of these doublet regimens because of the strict criterion for a confirmatory chest x-ray at 4 weeks to be considered a treatment responder. The time to progression of disease significantly favored gemcitabine compared with the paclitaxel reference arm.
(4.5 vs 3.5 mo; \( P = .003 \)). Overall survival at 1 and 2 years also tended to favor gemcitabine, but there were no significant differences for any of the groups compared with the reference arm (Table 2).

There was more variation among the regimens with respect to toxicities (Table 3). Grade 3/4 anemia and thrombocytopenia occurred significantly more often in the gemcitabine arm than in the reference arm. The higher incidence of hematologic toxicity in the gemcitabine arm may be due to the weekly doses of gemcitabine and more frequent monitoring (on days 1, 8, and 15 of the 28-day schedule). Gastrointestinal toxicities were similar among the three cisplatin-containing arms but occurred less frequently in the carboplatin-containing arm. Grade 3 sensory neurologic toxicity tended to occur more often in the carboplatin and gemcitabine arms.

Infections requiring hospitalization were less frequent in comparator treatment arms, particularly the carboplatin-containing arm, than in the reference treatment arm (cisplatin/paclitaxel), although the differences were not significant. Use of broad-spectrum antibiotics was also lower in the carboplatin-containing arm. An analysis of the total, aggregate worst degree of toxicity indicated fewer severe toxicities in the carboplatin-containing treatment arm, which was not significant when compared with the cisplatin/paclitaxel reference arm.

In summary, the E1594 clinical trial found no differences in the primary end point or in survival between the cisplatin/paclitaxel reference arm and each of the comparator treatment arms. The time to progression of disease was, however, significantly improved with the gemcitabine regimen, while the overall response rate to carboplatin/paclitaxel was worse than with the reference regimen, with the difference approaching statistical significance. Treatment decisions regarding use of one of these doublet regimens in patients with non-small-cell lung cancer, therefore, depends on other considerations, including cost-effectiveness, side effects and toxicities, and ease of administration. Other considerations may include the overall response rate and time to progression of disease.

**Evolving Treatment Strategies**

While the overall response rate in the gemcitabine arm of the E1594 clinical trial was comparable to the reference treatment arm, the higher incidence of hematologic toxicities may have been related to its use in combination with cisplatin 100 mg/m\(^2\), which is also hematotoxic, to the days 1, 8, and 15 administration regimen in a 28-day schedule, or to both. Administration of gemcitabine at 1,000 mg/m\(^2\) on days 1 and 8 of a 21-day schedule,[9] gemcitabine at 1,000 mg/m\(^2\) on days 1, 8, and 15 of a 28-day schedule,[10] or gemcitabine at 1,200 mg/m\(^2\) (with dose escalation) on days 1 and 8 of a 28-day schedule[11] with carboplatin has been shown to result in a good overall response rate and to be well tolerated.

**Conclusions**

In the United States, new regimens employing gemcitabine are emerging for the treatment of newly diagnosed patients with stage IIIIB or IV non-small-cell lung cancer (Figure 3). For patients with a good performance status, gemcitabine at 1,000 mg/m\(^2\) on days 1 and 8 plus carboplatin dosed at an area under the concentration-time curve (AUC) of 6 on day 1 of a 21-day schedule is being evaluated. In patients with a poor performance status, single-agent gemcitabine at 1,000 to 1,250 mg/m\(^2\) on days 1 and 8 in a 21-day schedule is being studied. Patients who relapse on either of the gemcitabine regimens would receive docetaxel 75 mg/m\(^2\) every 3 weeks.

**References:**


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