Advances in Treatment of Inoperable NSCLC: Gemcitabine Doublets—A Promising Alternative

Published on Physicians Practice (http://www.physicianspractice.com)

By Federico Cappuzzo, MD [2], Caio Max S. Rocha Lima, MD [3], and Mark R. Green, MD [4]

Gemcitabine (Gemzar) was originally approved for use in combination with cisplatin (Platinol) for the treatment of advanced non–small-cell lung cancer (NSCLC). Research began to focus on combining gemcitabine with newer agents.

Introduction

In the last decade, it has become clear that the use of effective systemic chemotherapy can improve patient survival, quality of life, and performance status compared with best supportive care for selected patients with advanced-stage non–small-cell lung cancer (NSCLC). Single-agent therapy with active drugs has been shown to produce response rates of 25% to 30%, reduce tumor burden, alleviate symptoms of disease, such as dyspnea and hemoptysis, and improve survival.[1-3]

Combination chemotherapy appears to provide even better control, yielding response rates of 30% to 40% and extending median survival to 6 to 12 months vs 4 to 8 months without chemotherapy.[4-12] Cisplatin (Platinol)-based combination regimens are considered the treatment of choice for NSCLC.[12] However, the availability of several new drugs that are active against NSCLC and also quite well tolerated has broadened the options for treatment.

Gemcitabine (Gemzar) is a particularly notable member of this new group of chemotherapeutic agents. With a database of more than 800 patients enrolled in phase II clinical trials, single-agent gemcitabine is one of the most widely studied drugs for the treatment of NSCLC. Externally validated response rates achieved with single-agent gemcitabine range from 20% to 26%.[13] One-year survival rates as high as 40% have been reported with gemcitabine chemotherapy in select patient groups.[13-18] Potentially important interactions of gemcitabine and radiation have also been recognized.[19-20]

Single-Agent Gemcitabine in NSCLC

In lung cancer patients, single-agent gemcitabine is usually administered at doses of 1,000 mg/m² to 1,250 mg/m² on days 1, 8, and 15 of a q28-day schedule.[14-16] Among the studies of single-agent gemcitabine, results have been notably consistent, with an aggregate response rate of approximately 21% and median survivals of 7 to 9.4 months. Two small studies included higher doses of gemcitabine (up to 1,700 mg/m²[21] and 2,800 mg/m²[22]), with little to suggest added benefit. In many cases, gemcitabine therapy improved disease-related symptoms. The toxicity profile was very acceptable.

In two small randomized studies, [17,18] gemcitabine produced survival rates that were essentially identical to platinum-based combination chemotherapy. Perng and coworkers treated 53 chemonaive patients with inoperable stage III (N = 14) or IV (N = 39) NSCLC with either gemcitabine 1,250 mg/m² on days 1, 8, and 15 or cisplatin (80 mg/m² on day 1) plus etoposide (80 mg/m² on days 1, 2, and 3) (N = 26). Response rates were 19.2% for patients receiving the gemcitabine regimen and 20.8% for patients given the cisplatin/etoposide regimen.[17] The median survival rate among patients receiving gemcitabine was 37 weeks compared with 48 weeks on the cisplatin combination. The 1-year survival rate in the gemcitabine arm was close to 40%. Similarly, European investigators assessed the same regimens, except that cisplatin and etoposide were both administered at 100 mg/m².[18] Again, the response and median survival rates were very similar between groups. Thus, single-agent gemcitabine appears to produce activity comparable to etoposide/cisplatin combination chemotherapy in the treatment of NSCLC.

Gemcitabine Plus Cisplatin

Phase II Trials
The combination of gemcitabine 1,000 mg/m² on days 1, 8, and 15 and cisplatin 100 mg/m² on either day 1, 2, or 15 has been evaluated in numerous phase II trials. Five selected phase II trials involving several hundred patients are representative.[23-27] All five studies involved untreated patients with stage III or IV NSCLC, although the ratio of patients with stage III vs IV disease varied widely. For instance, investigators in South Africa included 50 patients in their trial, among whom only 38% had stage IV disease.[26]

In comparison, 54% of patients in the Italian Lung Cancer Project (ILCP) trial,[24] and 81% of patients in the study by Sandler and colleagues had stage IV NSCLC.[25] This heterogeneity of disease stage, combined with slight differences in scheduling, may have been responsible for the reported spectrum of response and survival outcomes.[28] Response rates in these five trials ranged from 42% to 54%. Median survival ranged from 8.4 months to 14.3 months (Table 1). The major toxicity was reversible myelosuppression of short duration.

Overall, the results of these studies revealed the gemcitabine/cisplatin combination to be an effective regimen, producing favorable response rates and survival. Results of these phase II studies led to the initiation of pivotal randomized phase III trials of the cisplatin/gemcitabine combination.[29,30]

**Phase III Trials**

The Hoosier Oncology Group trial compared gemcitabine/cisplatin vs cisplatin alone in 522 patients with previously untreated, locally advanced or metastatic NSCLC.[29] Patients received either 100 mg/m² cisplatin on day 1 of a 28-day cycle (N = 262) or cisplatin 100 mg/m² on day 1 plus gemcitabine 1,000 mg/m² on days 1, 8, and 15 repeated q28 days (N = 260).

Response to the combination proved to be significantly superior to that of cisplatin alone: 30.4% vs 11.1% (P < .0001). Furthermore, there was a statistically significant advantage for the combination in terms of median response duration (5.6 months vs 3.7 months, P = .0013) and overall survival (P = .004).

Cardenal and colleagues in Spain compared the activity of an q3-week gemcitabine/cisplatin regimen with standard etoposide/cisplatin in the treatment of 135 patients with advanced NSCLC.[30] Regimens of either cis-platin 100 mg/m² on day 1 plus gemcitabine 1,250 mg/m² on days 1 and 8 or cisplatin 100 mg/m² on day 1 plus etoposide 100 mg/m² on days 1, 2, and 3 were administered on an q21-day schedule. The overall response rate for gemcitabine/cisplatin was statistically superior to that for etoposide/cisplatin (40.6% vs 21.9%; P = .02). In addition, time-to-disease progression was significantly greater with gemcitabine/cisplatin (6.9 months vs 4.3 months; P = .01). Median survival time was 8.7 months with gemcitabine/cisplatin and 7.2 months with etoposide/cisplatin (P = .18).

This trial supports the current widespread use of the better-tolerated 21-day schedule of gemcitabine/cisplatin, which again demonstrated an improved response rate and time-to-disease progression vs standard cisplatin/etoposide therapy.

The Italian Lung Cancer Project investigators tested the 4-week gemcita-bine/cisplatin regimen against the three-drug combination of mitomycin (Mutamycin)/ifosfamide (Ifex)/cisplatin.[31] In this study, 307 patients with stage IIIIB/IV NSCLC were randomly assigned to an q28-day treatment with either gemcitabine 1,000 mg/m² on days 1, 8, and 15 plus cisplatin 100 mg/m² on day 2 or mitomycin 6 mg/m²/ ifosfamide 3,000 mg/m² /mesna on day 1 plus cisplatin 100 mg/m² on day 2. Although there was no statistically significant difference in overall median survival (8.6 vs 9.6 months, P = .877), median time to progression (5.0 vs 4.8 months) or median time-to-treatment failure (4.0 vs 3.7 months), an improved response rate was observed in the gemcitabine/cisplatin arm (P = .029). This confirms the substantial activity of gemcitabine/cisplatin in patients with metastatic or poor prognosis stage IIIIB disease. Toxicity was comparable in the two arms.

**Figure 1** illustrates the 1-year survival advantages of gemcitabine/cisplatin (21- and 28-day schedules) relative to cisplatin/etoposide or cisplatin alone. This benefit was associated with equivalent or improved quality-of-life parameters for the gemcitabine-based therapy compared with the other regimens. The gemcitabine/cisplatin regimen also had a tolerable safety profile. The predominant toxicity was acute myelosuppression, generally marked by a short nadir and little clinical impact. Rates of febrile neutropenia and bleeding requiring transfusion were low, and hematologic toxicities generally resolved quickly.

Although thrombocytopenia was a frequent cause for dose reductions, full recovery generally occurred within the cycle period. This was true on both the 21-day and 28-day schedules. Other toxicities—including alopecia, sensory neuropathy, and diarrhea—were mild and transient. Overall, the gemcitabine/cisplatin regimen fared well in phase III comparisons, and was deemed to warrant further consideration in the treatment of advanced NSCLC.
New Doublets

Some of the toxicities observed with the gemcitabine/cisplatin combination—in particular nausea, vomiting, and renal dysfunction—can be directly attributed to cisplatin. This made the development of a gemcitabine/carboplatin (Paraplatin) regimen a high priority. With the emergence of several new non-platinum compounds that are active in lung cancer, the development of non-platinum-based gemcitabine combinations has also accelerated dramatically.

**Gemcitabine Plus Carboplatin**

In innumerable treatment settings, carboplatin has been shown to provide similar efficacy, decreased nonhematologic toxicity, and improved convenience relative to cisplatin. Initially, British investigators attempted to combine carboplatin with gemcitabine using a day 1, 8, and 15 gemcitabine schedule. Dose-limiting myelosuppression was reached at a carboplatin area under the curve (AUC) of 5.2 administered day 1 every 4 weeks. Responses were seen in 4 of 13 patients.

A similar schedule was tested by the Hoosier Oncology Group. However, the study was closed early due to severe hematologic toxicity. The first course of an q28-day regimen of 1,000 mg/m² gemcitabine delivered weekly for 3 weeks plus carboplatin given on day 1 at an AUC of 5 produced grade 3-4 thrombocytopenia in four of the first five patients treated. The day-15 dose of gemcitabine was held in four of seven patients. No objective responses were recorded and median survival time was 130 days.

Preliminary reports of subsequent studies of this combination that were presented at the 1999 meeting of the American Society of Clinical Oncology have proven to be more promising (Table 2). Although hematologic toxicity remained substantial, efficacy results were consistently positive. Despite high rates of grade 3-4 thrombocytopenia (~40% to 60%, with grade 4 toxicity in up to 50% of cases), bleeding episodes were rare. Grade 3-4 neutropenia occurred in 15% to approximately 40% of patients, but febrile neutropenia was infrequent. Objective response rates ranged from 32% to 51%. These findings suggest that gemcitabine/carboplatin is a feasible and active regimen for the treatment of NSCLC.

Due to the favorable results that occurred with a 21-day schedule of gemcitabine/cisplatin (including equivalent activity often with less myelotoxicity), several studies have examined this alternative dosing schedule with gemcitabine/carboplatin (Table 2). Using gemcitabine doses of 800 mg/m² to 1,250 mg/m² and carboplatin at AUCs of 5 to 6, these trials have reported response rates averaging 40% to 50%, with little evidence of grade 3-4 neutropenia or thrombocytopenia.

Iaffaioli and colleagues were the first to report the results of their dose-finding study that employed carboplatin at a fixed AUC of 5 plus escalating doses of gemcitabine in the treatment of chemotherapy-naive patients with stage IIIB to IV NSCLC. Gemcitabine was administered on days 1 and 8, beginning at 800 mg/m² and increasing by 100 mg/m² in cohorts of three patients until dose-limiting toxicity was observed. Carboplatin was given on day 8 and cycles were repeated every 4 weeks. Neutropenia—not the expected thrombocytopenia—was the dose-limiting toxicity, occurring in three of five patients at the 1,200 mg/m² dose level. The maximum-tolerated dose (MTD) of day 1 and 8 gemcitabine was 1,100 mg/m²/dose. The response rate was 50%, including four complete responses and nine partial responses among the 26 evaluable patients. Median duration of response was 13 months and the overall survival was 16 months. These results compared favorably to the activity of gemcitabine/cisplatin therapy.

Sederholm employed gemcitabine at doses of 1,200 mg/m² to 1,250 mg/m² on days 1 and 8 plus carboplatin at an AUC of 5 (N = 10) or 6 (N = 25) administered on day 1 with a 21-day cycle. At the lower dose levels, there were no episodes of grade 4 hematologic toxicity. At a gemcitabine dose of 1,250 mg/m² and carboplatin at an AUC of 6, grade 4 granulocytopenia or thrombocytopenia occurred after 4% and 7% of infusions, respectively. One patient (4%) died of pneumonia while neutropenic. The objective response rate of greater than 40% was encouraging.

In two additional studies using the day 1 and day 8 q3-week schedule, gemcitabine at a dose of 1,000 mg/m² was combined with carboplatin at an AUC of 5 or 5.5. Despite slightly lower gemcitabine doses, higher rates of hematologic toxicity occurred in both of these studies compared to those described previously. Toxicity still fell within the acceptable range. Overall response rates of 48% and 32% were reported.

These consistent results from multiple studies of the q3-week schedule of gemcitabine plus carboplatin demonstrate that this combination is well tolerated and active. The predominant toxicity is reversible myelosuppression, with little risk of febrile neutropenia or significant bleeding. Based on these findings, several phase III trials using the q3-week schedule of gemcitabine and carboplatin as one treatment arm are in development.
Gemcitabine Plus a Taxane

Combinations of gemcitabine plus a taxane are of great potential interest for the treatment of NSCLC. Both drugs have shown good single-agent activity in NSCLC, possess differing mechanisms of action, and for the most part, produce nonoverlapping toxicities. Therefore, the combination of gemcitabine/taxane might be expected to provide at least good additive activity with little risk of severe side effects. Numerous investigators have studied the combination in patients with a variety of tumor types, including NSCLC (Table 3 and Table 4).[42-50] Some of these studies will be reviewed here.

**Docetaxel (Taxotere)** In four phase I/II trials of docetaxel combined with gemcitabine, two studies used the q4-week schedule and two studies used an q3-week cycle.[42-45] The 28-day schedules employed 800 mg/m² gemcitabine on days 1, 8, and 15. In one study by Pawinski et al, a fixed 85 mg/m² docetaxel dose was added on day 15.[42] This regimen yielded a high rate of neutropenia (60%) and limited responses (12%) among patients with solid tumors.

In a second study, Spiridonidis and coworkers defined the MTD of docetaxel when combined with 800 mg/m² gemcitabine in previously treated patients with solid tumor.[43] Docetaxel was added at increasing doses, beginning at 45 mg/m² on either day 1 or 15. The day-15 schedule proved to be excessively toxic with severe thrombocytopenia and hepatic dysfunction. The investigators found the day-1 administration of docetaxel, along with gemcitabine on days 1, 8, and 15, to be better tolerated. Their recommended phase II dose of docetaxel was 100 mg/m² on day 1 in combination with gemcitabine at 800 mg/m² days 1, 8, and 15. Anti-tumor activity was observed in 9 of 21 (43%) previously treated patients with NSCLC.

Using the q21-day schedule of gemcitabine/docetaxel, Greek investigators treated 51 chemotherapy-naive, advanced NSCLC patients with gemcitabine 900 mg/m² on days 1 and 8 plus docetaxel 100 mg/m² on day 8.[44] With this regimen, grade 4 anemia and thrombocytopenia were rare; grade 3-4 neutropenia occurred in only 4 patients (8%). Partial responses were observed in 19 patients (37.5%), with a median duration of response of 5 months and median survival of 13 months. The actuarial 1-year survival was 50.7%.

Similar results were reported from Argentina,[45] where a regimen of 1,000 mg/m² gemcitabine on days 1 and 8, plus 75 mg/m² of docetaxel, yielded an objective response rate of 31%. Tolerable hematologic toxicity occurred in this study as well, with 39% of patients experiencing grade 3-4 neutropenia, and no severe or life-threatening thrombocytopenia in the 18 enrolled patients.

In a large randomized phase II trial involving 347 patients with advanced NSCLC, the activity of docetaxel/gemcitabine was tested against docetaxel/cisplatin.[46] In this trial, 100 mg/m² docetaxel on day 8 plus 1,100 mg/m² gemcitabine on days 1 and 8 produced objective response rates (34% vs 31%), median survival rates (11 months vs 12 months), and 1-year survival rates (41% vs 46%) similar to 100 mg/m² docetaxel (day 1) plus 80 mg/m² cisplatin (day 2). Both regimens included granulocyte colony-stimulating factor (G-CSF) support. The rate of grade 3-4 neutropenia with the docetaxel/gemcitabine combination was lower than in the docetaxel/cisplatin regimen (20% vs 34%), although febrile neutropenia developed more often with the gemcitabine combination. Grade 3-4 thrombocytopenia occurred at equal rates in the two groups: 2% with the gemcitabine regimen and 6% with the cisplatin regimen.

**Paclitaxel (Taxol)** In another article in this issue, you will find the preliminary results of an interim analysis of a phase III trial by Kosmidis comparing paclitaxel/gemcitabine and paclitaxel/carboplatin.[47] These investigators randomized 127 patients with advanced NSCLC to either 200 mg/m² q3-hour paclitaxel on day 1 plus 1 g/m² gemcitabine on days 1 and 8 or 200 mg/m² q3-hour paclitaxel on day 1 plus carboplatin at an AUC of 6 on day 1. Toxicities were extremely mild on both regimens. Low rates of significant neutropenia and neurotoxicity were reported: neutropenia 0% for the gemcitabine arm vs 4.8% for the carboplatin arm; neurotoxicity 0% for the gemcitabine arm vs 4.8% for the carboplatin arms. There was no life-threatening thrombocytopenia associated with either regimen. The response rate with the paclitaxel/gemcitabine combination was 37.5% vs 21.8% with paclitaxel/carboplatin. Additional accrual to this trial is ongoing and the final results will be awaited with great interest.

**Weekly scheduling** Gemcitabine combinations with paclitaxel have been examined using a weekly × 3 q4 weeks dosing schedule for both drugs (Table 4).[48-50] Escalating doses of both gemcitabine and docetaxel, each delivered on days 1 and 8 of an every 3-week cycle, have also been evaluated by Rizvi et al (Table 3).[48] Activity has been evident and myelosuppression was low among previously untreated patients. Fatigue, malaise, and asthenia were the most common dose-limiting toxicities. Based on the Rizvi data,[48] the Cancer and Leukemia Group B is currently...
testing gemcitabine 1,000 mg/m² on days 1 and 8 combined with docetaxel 40 mg/m² on days 1 and 8 as part of a randomized phase II trial in previously untreated patients with advanced NSCLC. Paclitaxel has been similarly combined with gemcitabine on a weekly schedule.[49,50] Einhorn et al administered escalating doses of gemcitabine (600 mg/m² to 1,000 mg/m²) plus paclitaxel (60 mg/m² to 135 mg/m² as a 3-hour infusion) for 3 consecutive weeks of a 4-week cycle to 31 patients with various cancers.[49] At doses up to 1,000 mg/m² gemcitabine and 110 mg/m² paclitaxel, nonhematologic toxicity was modest with no grade 3-4 toxic events. However, 13 of 28 patients experienced grade 3-4 neutropenia and one patient each had grade 3-4 thrombocytopenia and febrile neutropenia.

DeBraud et al, reporting for investigators from Italy and Switzerland, employed higher doses of gemcitabine (800 mg/m² to 1,750 mg/m²) plus similar doses of paclitaxel (60 mg/m² to 100 mg/m²) on the same weekly schedule for 3 of every 4 weeks.[50] A preliminary response rate of 59% was achieved without much risk of severe myelosuppression: six of 62 cycles (10%) produced grade 3 or 4 neutropenia, and only one cycle in 62 (2%) produced grade 3 thrombocytopenia. No grade 4 thrombocytopenia occurred. The MTD was not reached at the highest tested dose level.

Comparison of taxanes
In order to establish the relative benefit of a gemcitabine/docetaxel vs a gemcitabine/paclitaxel regimen, Natale and colleagues are carrying out a small randomized comparison of the two combinations. This trial, called ACORN 9901, will assign patients with advanced or metastatic NSCLC to one of the two combinations.[R. Natale, personal communication, June 2000.] Results of this trial may provide some insight into which taxane may be best combined with gemcitabine for the treatment of NSCLC.

Gemcitabine Plus Vinorelbine (Navelbine)
Gemcitabine/vinorelbine has been extensively evaluated for the treatment of patients with NSCLC. Both agents are active against NSCLC, can be delivered on an outpatient basis, and have differing mechanisms of action. The combination has been proven active against NSCLC in early phase I/II trials.[51] Schedules of both day 1, 8, and 15 every 4 weeks and day 1 and 8 every 3 weeks have been evaluated.

Investigators at the M. D. Anderson Cancer Center attempted to deliver both 1,000 mg/m² gemcitabine and 30 mg/m² vinorelbine,[52] using a day 1, 8, and 15 approach. Due to severe myelosuppression in the first 6 patients, doses were reduced to 900 mg/m² and 25 mg/m², respectively, in the 50 subsequent patients. Even at the reduced starting doses, however, 18% of cycles required further dose reductions or holding doses due to myelosuppression. Among 19 evaluable, previously untreated patients, 8 (42%) achieved a partial response. Chen and coworkers used still lower doses of vinorelbine 20 mg/m² followed by gemcitabine 800 mg/m² days 1, 8, and 15,[53] but still observed a 52% rate of grade 3-4 neutropenia and a 13% rate of grade 3-4 thrombocytopenia. Their reported overall response rate of 70% is the highest thus far reported by any investigators testing this two-drug combination.

Pirker et al administered vinorelbine 25 mg/m² followed by gemcitabine 1,200 mg/m² using the q3-week schedule.[54] Again, there was a significant amount of grade 3-4 neutropenia (55%) and thrombocytopenia (15%), as well as only a modest objective response rate of 19%. Hirsh et al used 1,000 mg/m² of gemcitabine followed by 25 mg/m² to 30 mg/m² of vinorelbine.[55] These investigators reported a response rate of 33% and minimal toxicity. It is uncertain whether the diminished toxicity reported by Hirsh et al is due to the sequence of gemcitabine followed by vinorelbine.

Experience using both gemcitabine and vinorelbine on days 1 and 8 on an q3-week cycle has also been reported. Lilenbaum et al used gemcitabine doses of 1,000 mg/m² to 1,250 mg/m² over 30 minutes followed by vinorelbine at 25 mg/m² over 6 minutes in previously untreated patients with advanced NSCLC. Tolerance was reportedly excellent[56] even in a small group of patients over age 70.[56] Gridelli et al used a similar schedule with doses of 1,000 mg/m² and 30 mg/m² for gemcitabine and vinorelbine, respectively.[57] Once again, the toxicity profile was favorable, as might have been predicted from the experience with a 21-day treatment cycle for other gemcitabine combinations. This 21-day schedule of the two-drug regimen is now being compared to vinorelbine alone in ongoing randomized phase III trials.

Conclusions
Non-platinum-containing combinations for the treatment of advanced NSCLC offer some potential benefits compared to traditional cisplatin-based chemotherapy. Gemcitabine doublets with taxanes, vinorelbine, or carboplatin produce response and survival rates similar to those achieved with
cisplatin-based combinations with lower rates of cisplatin-associated toxicities, such as anemia, renal dysfunction, and nausea/vomiting. Gemcitabine doublets can produce significant myelosuppression when drugs are administered on days 1, 8, and 15 of a q28-day schedule. Experience to date suggests that toxicity can be significantly reduced by administering the drugs on days 1 and 8, with recycling every 3 weeks.

Additional gemcitabine-based doublet regimens, including gemcitabine/irinotecan (Camptosar)[58] and gemcitabine/multitargeted antifolate (Alimta) (MTA),[59] have been developed. Both are currently in phase II testing in patients with chemonaive, advanced NSCLC. Three-drug regimens, including gemcitabine, are also being studied.[60]

Studies of gemcitabine combinations confirm the important potential of this agent in the treatment of patients with NSCLC. Over the next several years, additional information will emerge to more clearly define its broad role in the optimal treatment of patients with NSCLC.

References:


Links: