Gemcitabine and Nonplatinum Combinations in Non-Small-Cell Lung Cancer

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Introduction

Gemcitabine (Gemzar), docetaxel (Taxotere), paclitaxel (Taxol), and vinorelbine (Navelbine) are among the most active agents for the treatment of non-small-cell lung cancer (NSCLC). Each has been shown to produce objective responses in approximately 20% of previously untreated patients with advanced or metastatic disease and to improve survival when compared with best supportive care. When combined with a platinum compound, these agents have, to date, produced the best survival outcomes in non-small-cell lung cancer and represent the new standard of care for good performance status in patients with advanced or metastatic disease.

These new agents generally appear to be more active than platinum compounds. Gemcitabine, in particular, appears to be at the head of the class with respect to activity and patient tolerance. More than 500 patients were treated in six phase II clinical trials with gemcitabine 1.0-1.2 g/m² on days 1, 8, and 15 every 4 weeks. Reported objective response rates are in the range of 21% to 26%. Fewer than 7% of these patients suffered any grade 4 toxicity.

Three randomized clinical trials have shown that single-agent gemcitabine can produce response rates and survival outcomes equivalent to the combination regimens of cisplatin (Platinol)/etoposide[7,8] or cisplatin/vindesine (Eldisine)[9]. However, gemcitabine has considerably less toxicity and greater benefit with respect to improved quality of life and performance of daily activities. Therefore, investigators have hypothesized that gemcitabine could be combined with one of the other new agents to create novel nonplatinum doublet combinations with efficacy and/or toxicity profiles superior to that of standard platinum-containing combinations. This article summarizes the efforts to date that explore gemcitabine combined with docetaxel, paclitaxel, or vinorelbine.

Gemcitabine/Docetaxel Combinations

Gemcitabine with docetaxel was the first combination examined. In the initial two studies, docetaxel was added on day 1 or 15 to a standard day 1, 8, and 15 schedule of gemcitabine. Treatment was recycled every 28 days.

28-Day Schedules

Pawinski et al[10] reported the results of 30 courses of treatment in 11 patients (10 of whom had received prior chemotherapy) with a variety of tumor types. On the 28-day schedule, gemcitabine 800 mg/m² was administered on days 1, 8, and 15 with docetaxel 85 mg/m² on day 1. Grade 3/4 neutropenia occurred in 18 of the 30 courses (60%), including febrile neutropenia in 2 of the 11 patients. Grade 3/4 thrombocytopenia occurred in 5 of the 30 courses (17%), and grade 3 dermatitis or increased liver function tests (LFTs) occurred in one patient each. Six of the 11 patients required attenuation of the docetaxel dose. The authors concluded that it was not feasible to carry this dose and schedule forward to expanded phase II or phase III trials.

Similarly, Spiridonidis et al[11] explored escalating doses of docetaxel on day 1 or day 15 of a day 1,
8, and 15 schedule of gemcitabine 800 mg/m² every 28 days in 40 patients (39 with prior chemotherapy) with a variety of tumor types. Dose-limiting toxicity consisted primarily of grade 4 neutropenia in 40% of patients, febrile neutropenia in 7.5%, grade 3/4 thrombocytopenia in 22.5%, grade 3 asthenia in 17.5%, grade 3 flu-like symptoms in 10%, and grade 3 fluid retention in 7.5%. The maximum tolerated dose for docetaxel was higher when it was given on day 1 compared to day 15: 100 mg/m² vs 75 mg/m², respectively. Furthermore, successful delivery of the planned dose of docetaxel was 98% vs 74% for the two schedules, respectively.

Objective responses were reported in four of seven patients with previously treated breast cancer and in 9 of 21 patients with previously treated NSCLC (43% response rate, 95% confidence interval [CI]: 22% to 66%), including objective regressions in brain metastases in four patients. Similar to the Pawinski study, dose-limiting myelotoxicity most often occurred on or near day 15 of this schedule, frequently requiring dose attenuations or omissions in the planned day 15 dose of gemcitabine.

21-Day Schedules

Because of the frequent need to reduce or omit day 15 treatment in these 28-day schedules, investigators began to explore 21-day schedules in which gemcitabine could be given on days 1 and 8 with docetaxel on day 1 or 8 (Table 1).

Greek Lung Cancer Cooperative Group Study

Georgoulias et al[13] reported the results of a Greek Lung Cancer Cooperative Group study that explored this new schedule in 52 patients with previously untreated NSCLC. Gemcitabine 900 mg/m² was administered on days 1 and 8 combined with docetaxel 100 mg/m² on day 8. Granulocyte colony-stimulating factor (G-CSF [Neupogen]) was added to the regimen at 150 µg/m² on days 9 to 15. Data from 251 courses of treatment indicated that toxicity was relatively mild with grade 3/4 neutropenia, thrombocytopenia, or anemia in 20%, 8%, and 10% of patients, respectively, and febrile neutropenia in 8%. Grade 2 or 3 asthenia was reported in 17% and 2% of patients, respectively; fluid retention was ≤ grade 2 in 19% of patients.

Gemcitabine and docetaxel dose intensities were maintained at 600 mg/m²/wk and 33 mg/m²/wk, respectively (100% of planned dose intensity), and only 14 of 251 treatment courses were delayed secondary to toxicity. Objective responses were observed in 19 patients (36.5% response rate, 95% CI: 21.5% to 46.4%). The median response duration was 5.0 months, time to tumor progression 7.0 months, and survival 8.5 months; 1-year survival was 42%.

Similar Results From Two Studies

Two additional studies exploring this 21-day schedule soon followed. Rubio et al[14] reported the results of a study by Argentinian investigators using gemcitabine 1,000 mg/m² on days 1 and 8 combined with docetaxel 75 mg/m² on day 8 in 18 NSCLC patients. Hematologic toxicity was moderate with grade 3/4 neutropenia and thrombocytopenia occurring in 39% and 0% of courses, respectively. Objective responses were observed in 31% of patients.

Similar results were reported by Rebattu et al[15] with gemcitabine 1,000 mg/m² on days 1 and 8 combined with docetaxel 85 mg/m² on day 8 in 36 NSCLC patients. Grade 3/4 neutropenia and thrombocytopenia occurred in 50% and 5%, respectively, of courses. Objective responses were documented in 30% of evaluable patients.

Higher Dose Intensity

The rationale of changing from a day 1, 8, and 15 every-4-week schedule to a day 1 and 8 every-3-week schedule in gemcitabine-based studies recently received support from a randomized trial by Soto Parra et al.[16] In this study, patients received cisplatin 70 mg/m² on day 2 of either schedule with gemcitabine 1,000 mg/m².

The relative dose intensity (calculated as mg/m²/wk) of gemcitabine was higher with the 3-week schedule than with the 4-week schedule 589 mg/m²/wk compared to 564 mg/m²/wk, respectively.
The lower dose intensity of the 4-week schedule resulted from forced reductions or omissions of gemcitabine dosing on day 8 or 15 of the schedule in 17% and 80% of courses, respectively. In spite of the higher dose intensity of the 3-week schedule, grade 3/4 neutropenia, thrombocytopenia, and nonhematologic toxicity was significantly lower than with the 4-week schedule. Furthermore, the response rate was higher with the 3-week compared with the 4-week schedule (55% vs 40%, respectively), although the difference was not statistically significant.

### Cisplatin/Docetaxel Comparisons

The Greek Lung Cancer Study Group[17] was the first to compare a new gemcitabine/docetaxel combination to a platinum-based combination, cisplatin/docetaxel (Table 2). A total of 347 patients with advanced or metastatic NSCLC were randomized and treated on the every-3-week schedule. The first group (180 patients) received cisplatin 80 mg/m² on day 2 combined with docetaxel 100 mg/m² on day 1; the second group (167 patients) received gemcitabine 1,100 mg/m² on days 1 and 8 combined with docetaxel 100 mg/m² on day 8. To decrease the severity of granulocytopenia expected with these moderately intensive treatments, G-CSF was administered on days 3 to 9 of the platinum-based regimen and on days 9 to 15 of the gemcitabine-based regimen.

A comparison of the toxicities of the cisplatin/docetaxel vs gemcitabine/docetaxel regimens revealed a higher rate of grade 3/4 neutropenia with the former (34% vs 20%, respectively, \( P = .03 \)) but a higher incidence of febrile neutropenia with the latter (29% vs 17%, respectively, \( P = .004 \)). There were no significant differences between the two regimens with respect to grade 3/4 thrombocytopenia (2% vs 4%, respectively), anemia (6% vs 4%, respectively), or fatigue (30% vs 33%, respectively).

Furthermore, analysis of therapeutic end points revealed no statistically significant differences in response rates (31% vs 34%), median time to progression (8 months each), median survival (12 months vs 11 months), or 1-year survival (46% vs 41%). Although firm conclusions cannot be reached from this randomized phase II trial, it is the first trial to demonstrate that a nonplatinum-based regimen (gemcitabine/docetaxel) may be equivalent to a platinum-based regimen with respect to efficacy.

### 2-Week Schedule

Several groups of investigators have explored gemcitabine combined with docetaxel or paclitaxel given together every 2 weeks.[18,19] However, the extraordinarily high doses of gemcitabine achievable with this unconventional schedule (2,500-3,000 mg/m²) strongly implies a fundamental change in the drug's pharmacodynamic properties. Unfortunately, there is not sufficient information to conclude that its efficacy in non-small-cell lung cancer is not also significantly changed by this novel schedule.

### Gemcitabine/Paclitaxel Combinations

Four groups have investigated gemcitabine/paclitaxel combinations (Table 3).

#### Prior Chemotherapy

Androulakis et al[20] was the first to report the results of a phase II trial with gemcitabine 900 mg/m² on days 1 and 8 every 3 weeks combined with paclitaxel 175 mg/m² on day 8 in 49 patients previously treated with cisplatin or docetaxel for recurrent NSCLC. Hematologic toxicity was mild with grade 3/4 neutropenia or thrombocytopenia in only 12% and 2% of patients, respectively. Dose-limiting toxicity consisted of grade 2/3 asthenia (51%) or neuropathy (32%), respectively. Objective responses were reported in 18% of patients in this salvage setting.

### Chemonaive Patients

Giaccone and colleagues[21] investigated gemcitabine 1,000 mg/m² on days 1 and 8 every 3 weeks with paclitaxel in doses ranging from 150 to 200 mg/m² on day 1 in 49 previously untreated patients
with NSCLC. Grade 4 neutropenia or thrombocytopenia occurred in only 12% and 3.5%, respectively, of patients while objective responses were observed in 24%.

More recently, Monnier et al[22] and Auerbach et al[23] reported the preliminary results of their studies with gemcitabine 1,000 mg/m² on days 1 and 8 every 3 weeks with paclitaxel to 200 mg/m² (Monnier) or 175 mg/m² (Auerbach) on day 1 in 40 and 20 patients, respectively, with previously untreated NSCLC. Toxicity data were reported in the Monnier study with grade 4 neutropenia occurring in only 5% of patients and grade 4 thrombocytopenia in only 1%. Objective responses were reported in 35% and 47% of these two studies, respectively.

**Comparison to Carboplatin/Paclitaxel**

Kosmidis et al[24] were the first to report the results of a randomized clinical trial comparing the nonplatinum combination of gemcitabine/paclitaxel to a standard second-generation platinum-based regimen, carboplatin (Paraplatin)/paclitaxel, in patients with previously untreated advanced or metastatic NSCLC (Table 4).

Patients were randomized to receive either paclitaxel 200 mg/m² on day 1 with gemcitabine 1 g/m² on days 1 and 8 every 3 weeks or paclitaxel 200 mg/m² on day 1 with carboplatin at an area under the concentration-time curve (AUC) of 6 every 3 weeks. There were no statistically significant differences between the two arms of the trial with respect to grade 3/4 neutropenia (10.5% vs 9.6%), thrombocytopenia (1.2% each), or anemia (1.9% vs 3.6%) or grade 3 neuropathy (6.2% vs 5.4%). Although the results favored the nonplatinum regimen, there were no statistically significant differences in efficacy end points between gemcitabine/paclitaxel or carboplatin/paclitaxel with respect to (respectively) response rate (36.5% vs 28.7%), median time to tumor progression (7.2 months vs 6.9 months), median survival (12.3 months vs 10.7 months), or 1-year survival (51.3% vs 41.3%).

This, therefore, represented the second randomized clinical trial that demonstrated that nonplatinum combinations of novel agents can produce toxicity and survival results at least equal to the results previously achievable only with standard platinum-based regimens.

**Gemcitabine/Taxane Combinations: Novel Weekly Schedules**

Since more frequent dosing schedules often improve the efficacy of phase-specific cytotoxic agents and the opportunity for enhanced interaction with radiation therapy and other frequently dosed chemotherapeutic agents, there has been great interest in exploring weekly administration schedules with the taxanes.

**Paclitaxel**

Paclitaxel was the first taxane to be studied on a weekly schedule. Loffler et al[25] examined paclitaxel in doses ranging from 40 mg/m² to 90 mg/m² given as a 1-hour intravenous infusion weekly for 6 weeks in 50 previously treated patients with a variety of malignancies. Overall toxicity was mild with no grade 4 hematologic or grade 3 nonhematologic toxicity. In fact, at the maximum dose studied (90 mg/m²), grade 3 leukopenia was observed in only one of 10 patients. Objective responses were documented in 15 of 50 patients (30% response rate).

Ackerley[26] conducted a more formal phase I/II clinical trial of weekly paclitaxel given as a 3-hour infusion with doses from 100 mg/m²/wk to 200 mg/m²/wk in 26 previously untreated patients with NSCLC. The goal of this study was to define a maximum tolerated dose that could be maintained for 6 consecutive weeks. Doses of 135-150 mg/m²/wk were maintained in all six patients and 175 mg/m²/wk was maintained in four. Dose-limiting toxicity consisted primarily of neutropenia and cumulative neuropathy at the 200 mg/m²/wk dose level. Hematologic toxicity was mild at the lower recommended dose levels, and neuropathy occurred primarily after several weeks of treatment. Objective responses were documented in 9 of 24 evaluable patients (38% response rate).

**Docetaxel**
Docetaxel has also been studied on a weekly schedule. Peacock et al[27] investigated docetaxel doses ranging from 20 mg/m² to 52 mg/m² weekly for 6 consecutive weeks in 38 patients with advanced chemotherapy refractory malignancies. Notably, 23 of the 38 patients had previously received paclitaxel.

Myelosuppression was not a dose-limiting toxicity at any of the doses tested. Only five episodes of grade 3 leukopenia and no grade 4 leukopenia were observed in over 280 courses of treatment. Dose-limiting toxicity consisted primarily of grade 3 fatigue and asthenia, which was observed in all three patients treated at 52 mg/m²/wk and in 2 of 10 patients treated at 43 mg/m²/wk. Other grade 3 toxicities included severe dermatitis (acral erythema) at the 43 mg/m²/wk dose level. At weekly doses as high as 36 mg/m²/wk, docetaxel was extremely well tolerated with rare grade 3 or 4 toxicities even in previously treated patients. Although this group of patients had received prior chemotherapy, including paclitaxel, several objective responses were observed in patients with breast cancer or non-Hodgkin's lymphoma.

**Weekly Gemcitabine/Docetaxel**

Because of the encouraging data with a weekly schedule of paclitaxel or docetaxel, several investigators have explored the combination of weekly gemcitabine plus a taxane. Two groups have studied weekly gemcitabine/docetaxel.

Rizvi et al[29] conducted a phase I study of gemcitabine 800-1,250 mg/m² combined with docetaxel 30-40 mg/m² on days 1 and 8 every 3 weeks in 26 patients with advanced cancers. Grade 3/4 neutropenia, observed in 7 of 26 patients (27%), was the most common toxicity. However, all seven patients had received two or more prior chemotherapy regimens whereas none of 11 previously untreated patients experienced grade 3/4 neutropenia. No significant hepatotoxicity, fluid retention, or neuropathy was observed. Two objective responses (partial responses) were documented in five patients with NSCLC, including one previously treated with cisplatin/etoposide and vinorelbine and one previously untreated.

**Escalating Docetaxel**

A small pilot study was conducted at the Cedars-Sinai Comprehensive Cancer Center in which we initially fixed the dose of gemcitabine at 1,000 mg/m² and combined it with docetaxel in doses escalating from 30 mg/m² to 35 mg/m² to 40 mg/m². No grade 3/4 hematologic toxicity or grade 2/4 nonhematologic toxicity (except alopecia) was observed in 27 courses of treatment (six patients) at the 30-35 mg/m² dose level of docetaxel. Toxicity in 11 treatment courses (four patients) at the 40 mg/m² dose level of docetaxel included grade 3 neutropenia in one course and grade 2 asthenia/fatigue in three courses; mild leg edema occurred in one of the four patients.

Gemcitabine was increased to 1,200 mg/m² with docetaxel 40 mg/m² with no grade 4 hematologic or grade 3/4 nonhematologic toxicity observed in seven treatment courses administered to two patients. Patients were given 4 mg dexamethasone to take orally on the day before, day of, and day after chemotherapy.

**Weekly Gemcitabine/Paclitaxel**

Four groups have studied weekly gemcitabine and paclitaxel. Einhorn et al[30] reported preliminary results in 31 patients with a variety of malignancies. Gemcitabine was given in doses ranging from 600 mg/m² to 1,000 mg/m² combined with paclitaxel in doses ranging from 60 mg/m² to 130 mg/m²/3 h on days 1, 8, and 15 every 4 weeks Overall the regimen was well tolerated. Cumulative neurotoxicity was dose-limiting at a paclitaxel dose level of 135 mg/m²/wk and was mild to moderate below that level. Grade 4 neutropenia was observed in three patients (10%), and there was one episode of neutropenic fever.

Subsequently, the recommended phase II dose level of gemcitabine 1,000 mg/m²/wk combined with paclitaxel 110 mg/m²/wk on 3 out of every 4 weeks was studied by the Hoosier Oncology Group in 42 previously untreated NSCLC patients.[31] Grade 3/4 neutropenia occurred in 43% of patients and
three patients died unexpectedly from febrile neutropenia. An additional patient died of pulmonary toxicity. Although the overall response rate was 37%, the 1-year survival was only 26%, primarily due to the unexpectedly high toxic death rate. Poor patient selection was cited as a possible contributing factor to these discouraging results.

**Encouraging Results**

DePas et al.[32] reporting for an Italian/Swiss group, conducted a phase I/II trial of gemcitabine 800-2,000 mg/m²/wk and paclitaxel 60-100 mg/m²/wk on 3 consecutive weeks out of every 4 weeks in 30 NSCLC patients. Hematologic toxicity was very mild with grade 3/4 neutropenia occurring only at the highest dose level studied and overall in only 10% of patients. The objective response rate was 43%.

We conducted another small pilot study at Cedar-Sinai Comprehensive Cancer center. Gemcitabine 800 mg/m²/wk to 1,200 mg/m²/wk and paclitaxel 80 mg/m²/wk to 120 mg/m²/wk for 2 out of every 3 weeks was given to 11 NSCLC patients. Grade 3/4 neutropenia occurred in 27% of patients and grade 3 neuropathy was observed in only one patient in the first three treatment cycles. There was no grade 3/4 thrombocytopenia; five patients (45%) achieved a partial response.

**Weekly Gemcitabine/Docetaxel vs Weekly Gemcitabine/Paclitaxel**

**ACORN Trial**

Based on the above experience with weekly gemcitabine/taxane combinations, we initiated a randomized phase II trial of weekly gemcitabine/docetaxel vs weekly gemcitabine/paclitaxel in patients with advanced or metastatic NSCLC among a group of primarily community-based medical oncologists called the American Clinical Oncology Research Network (ACORN) (Figure 1). Gemcitabine 1,200 mg/m² on days 1 and 8 every 3 weeks is given in both arms of the study.

**Methods**

In arm A, patients receive docetaxel 40 mg/m² and in arm B they receive paclitaxel 120 mg/m² on the same days as gemcitabine. Patients are stratified according to stage (IIIB vs IV), sex, performance status (PS 0-1 vs 2), and weight loss (≤ 5% vs > 5% prior weight loss) prior to randomization. Quality of life and differences in response rate and toxicity, with a special emphasis on taxane-associated asthenia and neuropathy and the impact of activities of daily living, are the primary study end points. Time to tumor progression and survival are secondary end points.

**Preliminary Results**

To date, 51 patients have been entered into the study, 25 on arm A and 26 on arm B, and have received 188 courses of treatment. Toxicities in the first two cycles of treatment have been mild with grade 4 neutropenia in four (16%) patients on arm A and in two (8%) patients on arm B. Grade 3/4 asthenia/fatigue has occurred in four (16%) patients on arm A and in two (8%) patients on arm B. Grade 3/4 neuropathy has occurred in three (12%) patients on arm B. Preliminary response rates are 44% and 35% on arms A and B, respectively. The study is targeted to accrue at least 75 evaluable patients per arm (total 150 patients).

**Gemcitabine/Vinorelbine Combinations**

One of the most widely explored nonplatinum combinations is weekly gemcitabine and vinorelbine. Seven phase II trials examined both drugs administered on days 1, 8, and 15 every 4 weeks.[33-39] Gemcitabine 1,000 mg/m² and vinorelbine 25 mg/m² were the most commonly used doses. Myelosuppression was the most common dose-limiting toxicity, with grade 3/4 neutropenia occurring in 10% to 50% of patients. Other adverse effects included fevers, myalgias, thromboses, and grade 1-3 elevated LFTs in 5% to 15% of patients. The near absence of alopecia is especially notable. Objective response rates varied from 19% to 70% with most in the 20% to 30% range.
Similar to the experience with gemcitabine/taxane combinations, alteration to a day 1 and 8
every-3-week schedule resulted in increased dose intensity (calculated on a mg/m²/wk basis) and
less severe toxicity. At least seven phase II trials examined both drugs administered on days 1 and 8
every 3 weeks.[40-46] In most studies, the dose of gemcitabine could be increased to 1,200 mg/m²;
in three of the seven studies, the dose of vinorelbine was increased from 25 mg/m² to 30 mg/m².

Myelosuppression remained the most common dose-limiting toxicity but appeared to be less than
that seen on the days 1, 8, and 15 every-4-week schedule. Grade 3/4 neutropenia occurred in 8% to
37% of patients. Fevers, myalgias, thromboses, and grade 1-3 elevated LFTs continued to occur in
5% to 15% of patients; alopecia was uncommon. Objective response rates also appeared to be
slightly higher than with the 4-week schedule, ranging from 27% to 41%.

Conclusions

More than 100 clinical trials conducted by investigators worldwide over the past 8 years have served
to define and expand the role of gemcitabine in the treatment of non-small-cell lung cancer. Clearly,
it is one of the most active and best tolerated drugs for the treatment of this disease. Its moderate
toxicity profile has allowed it to be combined with cisplatin, carboplatin, and the other new active
agents docetaxel, paclitaxel, and vinorelbine.

Gemcitabine combined with cisplatin or carboplatin ranks among the most active platinum-based
combinations in NSCLC. Several new nonplatinum gemcitabine-based combinations reviewed here
compare very favorably to platinum-based combinations with respect to toxicity and efficacy.
Changing the schedule of administration of gemcitabine from days 1, 8, and 15 every 4 weeks to
days 1 and 8 every 3 weeks appears to allow greater dose intensity with less severe toxicity and
slightly greater efficacy.

Coadministration of docetaxel, paclitaxel, or vinorelbine combined with gemcitabine on days 1 and 8
every 3 weeks is a very promising approach. In addition to a lower incidence of severe neutropenia,
these three agents protect against gemcitabine-associated thrombocytopenia. Interestingly,
paclitaxel given weekly with gemcitabine may produce less neurotoxicity than when it is given every
3 weeks with carboplatin.

Additional clinical trials are needed to better define doses and schedules of administration and to
confirm these promising preliminary observations. However, data presented in this review suggest
that gemcitabine-based combinations are emerging as a new standard for the treatment of
non-small-cell lung cancer.

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