Gemcitabine-Containing Regimens vs Others in First-Line Treatment of NSCLC

Review Article [1] | July 01, 2004
By Ronald B. Natale, MD [2]

Standard first-line chemotherapy regimens in advanced non-small-cell lung cancer (NSCLC) include carboplatin (Paraplatin)/paclitaxel, cisplatin/docetaxel (Taxotere), cisplatin/gemcitabine (Gemzar), and cisplatin/vinorelbine (Navelbine). An informal meta-analysis of 13 randomized trials of these regimens in NSCLC indicates no marked differences in terms of response rates or survival, but toxicity advantages with cisplatin/gemcitabine and cisplatin/vinorelbine regimens. An informal meta-analysis to assess the feasibility of substituting carboplatin for cisplatin in combination with gemcitabine or docetaxel shows no marked differences in efficacy between cisplatin- and carboplatin-containing regimens, although a slight trend favoring carboplatin/gemcitabine treatment may be observed; comparison of toxicity profiles among carboplatin-based regimens suggests advantages for carboplatin/gemcitabine treatment. A formal meta-analysis of 13 trials comparing gemcitabine/platinum combinations with other platinum-based regimens in NSCLC indicates significant improvements in progression-free survival and overall survival with gemcitabine/platinum treatment. On balance, available data suggest that carboplatin/gemcitabine may be the first-line option with the best therapeutic index.

Results of randomized clinical trials have established carboplatin (Paraplatin)/paclitaxel, cisplatin/gemcitabine (Gemzar), cisplatin/docetaxel (Taxotere), and cisplatin/vinorelbine (Navelbine) as standard first-line treatments for advanced/metastatic non-small-cell lung cancer (NSCLC). To address the relative merits of these regimens, an informal meta-analysis of efficacy and toxicity findings in randomized trials evaluating these regimens was performed. Similarly, an informal meta-analysis was performed to compare carboplatin-containing regimens with cisplatin-containing regimens to assess the potential merits of replacing cisplatin with carboplatin in combination with gemcitabine or docetaxel. In addition, a formal meta-analysis of trials comparing gemcitabine/platinum regimens with other platinum-based regimens in NSCLC has been performed with regard to progression-free survival and overall survival. In Informal Meta-analysis of Standard First-Line Regimens, our informal meta-analysis included 13 major randomized trials of carboplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/docetaxel, or cisplatin/vinorelbine as first-line regimens in advanced NSCLC; 12 of the trials had enrollment greater than 150 patients. Select results from these trials-consisting of objective response rate, median and 1-year survival, and major toxicities-were weighted for patient accrual, mathematically averaged, and compared. The 18 treatment arms included in the analysis are shown in Table 1.[1-12] The comparison of efficacy outcomes is shown in Table 2. Objective response rates were similar for the four regimens, ranging from 24% to 30%. Survival outcomes also showed little difference among regimens, with median duration of survival ranging from 8.6 to 9.1 months and 1-year survival ranging from 37% to 39%. These findings are consistent with those reported by Schiller et al in the Eastern Cooperative Oncology Group (ECOG) 1594 trial, which showed no significant differences in overall survival (and nearly superimposed survival curves) with cisplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/docetaxel, and carboplatin/paclitaxel.[3] and with the Southwest Oncology Group comparing carboplatin/paclitaxel to cisplatin/vinorelbine.[2]
The comparison of toxicities is shown in Table 3. The lowest rate of grade 4 granulocytopenia is seen with carboplatin/paclitaxel (15%) and the highest with cisplatin/docetaxel (35%). Rates of febrile
neutropenia ranged from 1% to 2% with carboplatin/paclitaxel and cisplatin/gemcitabine and from 4% to 5% with cisplatin/docetaxel and cisplatin/vinorelbine. The highest rate of grade 4 thrombocytopenia is observed with cisplatin/gemcitabine. It is important to note, however, both that this thrombocytopenia is characteristically transient and does not result in serious bleeding complications and that the six cisplatin/gemcitabine arms included in the analysis reflect use of gemcitabine on a schedule of days 1, 8, and 15 every 28 days. (Note that the cisplatin dose of 100 mg/m² in some of trials was higher than what is normally used in actual practice; cisplatin doses > 80 mg/m² only add incrementally more toxicity without efficacy.) With regard to the latter, hematologic toxicity is markedly reduced with no loss of efficacy when gemcitabine is given in the now-standard schedule of day 1 and 8 every 21 days. For example, a comparison of gemcitabine at 1,000 mg/m² on days 1, 8, and 15 every 28 days or 1,000 mg/m² on days 1 and 18 every 21 days plus cisplatin at 70 mg/m² on day 2 with both gemcitabine regimens showed that treatment with the 21-day schedule was associated with an increase in dose intensity of both drugs (due to improved delivery), a reduction in neutropenia (25% vs 35%), a reduction in thrombocytopenia (7% vs 40%), an increase in anemia (10% vs 0%, due to more frequent dosing of cisplatin), reduced nonhematologic toxicity (25% vs 33%), and a numeric but nonsignificant improvement in response rate (55% vs 40%).[13] With regard to nonhematologic toxicities, grade 3/4 neurologic toxicity is most common with carboplatin/paclitaxel, likely reflecting the increased risk with paclitaxel given on a 21-day schedule, with rates for the cisplatin-containing combinations reflecting the usual 6% to 10% rate of grade 3 neurologic toxicity seen with cisplatin. The rate of grade 3/4 arthralgias/myalgias is also highest with carboplatin/paclitaxel, likely reflecting the generally self-limiting and manageable toxicity that occurs on days 3 to 5 after paclitaxel administration, and lowest with cisplatin/gemcitabine. Alopecia of any grade is far more common with taxane-containing regimens than with cisplatin/gemcitabine or cisplatin/vinorelbine. Cisplatin-induced nephrotoxicity and gastrointestinal toxicity have also been reported in clinical trials.

Informal Meta-analysis: Can Carboplatin Replace Cisplatin in Combination With Gemcitabine or Docetaxel? It is unclear whether cisplatin-containing combinations with docetaxel or gemcitabine are superior to carboplatin-containing combinations. The findings of the TAX 326 trial, which showed a survival advantage of cisplatin/docetaxel over cisplatin/vinorelbine and no difference in this regard between cisplatin/vinorelbine and carboplatin/docetaxel regimens, are sometimes interpreted to indicate an advantage of cisplatin/docetaxel over carboplatin/docetaxel.[9] However, a number of trials have shown no difference between cisplatin- and carboplatin-containing regimens, including a trial comparing cisplatin/gemcitabine and carboplatin/gemcitabine.[14] with many data indicating that carboplatin-containing regimens are better tolerated.
We performed a meta-analysis of 13 trials involving 17 arms of first-line treatment with carboplatin/ paclitaxel, cisplatin/gemcitabine, carboplatin/ gemcitabine, cisplatin/docetaxel, and carboplatin/docetaxel (Table 4).[1-10,14-16] Therapeutic outcome comparisons show no marked difference between cisplatin/ gemcitabine and carboplatin/gemcitabine treatments, with perhaps some indication of trends favoring the latter (Table 5). There appears to be little difference between cisplatin/ docetaxel and carboplatin/docetaxel in terms of patient survival. Comparison of toxicities for carboplatin in combination with paclitaxel, gemcitabine, or docetaxel-the three most widely used carboplatin-containing regimens in the United States-shows advantages of the carboplatin/gemcitabine regimen over one or both other regimens in terms of granulocytopenia, neurologic toxicity, arthralgias/ myalgias, and alopecia (Table 6).
Conclusions

The use of two-drug platinum-based regimens have improved survival in advanced NSCLC. Our informal meta-analysis of trials evaluating carboplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/docetaxel, and cisplatin/vinorelbine indicates comparable efficacy of the regimens in terms of response rate, time to disease progression, and survival, with some advantages in terms of toxicity accruing to the regimens not containing taxanes. It also appears that carboplatin could be substituted for cisplatin in combination with gemcitabine or docetaxel without loss of effectiveness and with advantages in terms of toxicity and ease of drug administration. In this regard, the data may be particularly strong in favor of the carboplatin/gemcitabine combination, which appears to have the best therapeutic index of the platinum-based combinations. A recent formal meta-analysis indeed suggests that there are efficacy advantages to gemcitabine/platinum combinations compared with other platinum-based regimens in the treatment of NSCLC. Le Chevalier et al performed a meta-analysis of overall survival and time to disease progression in randomized trials comparing combinations of gemcitabine with carboplatin or cisplatin against a platinum-based regimen.[17] Thirteen trials were identified for the analysis, representing a total population of 4,556 patients. A total of 17 comparators were identified, including 12 platinum-based doublets (6 cisplatin/vinorelbine, 2 cisplatin/paclitaxel, 2 carboplatin/paclitaxel, 1 cisplatin/docetaxel, and 1 cisplatin/etoposide), 4 platinum-based triplets (mitomycin/vinorelbine/cisplatin or mitomycin/ifosfamide/cisplatin), and 1 singleagent cisplatin regimen. Hazard ratios were calculated using a fixed-effects model, with statistical heterogeneity being addressed using a random-effects model when appropriate, and absolute treatment benefit at 1 year was estimated. For overall survival, there was a significant reduction in mortality in favor of the gemcitabine-platinum arms versus platinum-based comparator arms; the hazard ratio for gemcitabine-based treatment was 0.90 (95% confidence interval [CI] = 0.84-0.96, \(P < .001\)), and the absolute survival advantage at 1-year was 3.9%. There was also a significant improvement in time to disease progression in favor of gemcitabine regimens; the hazard ratio was 0.87 (95% CI = 0.82-0.93, \(P < .001\)), and the absolute improvement in progression-free survival at 1-year was 4.2%. Although the superiority of any one of the currently accepted regimens for first-line treatment of advanced NSCLC has not been clearly defined by individual clinical trials,
analysis of available data in aggregate suggests that there may indeed be differences in effectiveness, tolerability, and toxicity among these regimens. On the basis of informal meta-analyses and the formal meta-analysis conducted by Le Chevalier et al,[17] it would appear that gemcitabine/platinum regimens pose an advantage in terms of therapeutic response and that gemcitabine/ carboplatin may be considered the preferred regimen on the basis of its overall efficacy and toxicity profiles.

**Disclosures:** The author has no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

**References:**


Source URL: http://www.physicianspractice.com/review-article/gemcitabine-containing-regimens-vs-others-first-line-treatment-nsclc

Links: