Gemcitabine in Combination With New Platinum Compounds: An Update

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Combinations of gemcitabine (Gemzar) with cisplatin (Platinol) are among the most active new chemotherapy regimens developed for advanced non-small-cell lung cancer. Carboplatin (Paraplatin) is a platinum analog.

Introduction

A number of randomized trials and meta-analyses have concluded that platinum-based therapy results in improved survival, symptom control, and quality of life compared to patients receiving supportive care alone. In a Cox multivariate analysis of approximately 2,300 cases of advanced non-small-cell lung cancer treated on studies of the Southwest Oncology Group (SWOG), platinum-based chemotherapy emerged as an independent predictive factor for improved survival, along with performance status and female gender.[1] In fact, randomized cooperative group studies have failed to demonstrate that adding another chemotherapeutic agent or agents to cisplatin (Platinol) improves survival compared to cisplatin alone.[2,3] However, this perspective is now changing.

Recently, several new chemotherapeutic agents such as gemcitabine (Gemzar), paclitaxel (Taxol), docetaxel (Taxotere), vinorelbine (Navelbine), and irinotecan (CPT-11, Camptosar) have demonstrated considerable single-agent activity in non-small-cell lung cancer. In randomized trials, these new agents, in combination with platinum compounds, have demonstrated improved response rates or survival compared to cisplatin alone or older platinum-based combinations. Combinations of gemcitabine and cisplatin are theoretically attractive due to preclinical synergism related in part to inhibition of repair of platinum-induced DNA damage, and have proven to be among the most active in clinical studies.

Gemcitabine and Cisplatin

The most common dose and schedule has been gemcitabine delivered on days 1, 8, and 15, with cisplatin given on either days 1, 2, or 15 of a 28-day schedule. In a recent phase III trial by Sandler et al,[4] this 28-day schedule of gemcitabine (1,000 mg/m$^2$ on days 1, 8, and 15) plus cisplatin (100 mg/m$^2$ on day 1) was compared to cisplatin alone in patients with advanced non-small-cell lung cancer.[4] Both response rate (30% vs 11%) and median survival (9 vs 6 months) were increased in the combination arm. As in most studies using this 28-day schedule, thrombocytopenia was dose-limiting, commonly resulting in omission of the day 15 gemcitabine dose (Table 1). Grade 4 thrombocytopenia occurred in 28% of patients receiving the combination; 22% received platelet transfusions. Similarly, in the phase III trial of Crino et al,[5] in which gemcitabine was delivered on days 1, 8, and 15, and cisplatin was given on day 2, grade 4 thrombocytopenia was reported in 38% of patients, while 15% received platelet transfusions.[5]

In contrast, the Spanish Lung Cancer Group[6] conducted a trial of a 21-day schedule delivering gemcitabine at 1,250 mg/m$^2$ on days 1 and 8 and cisplatin at 100 mg/m$^2$ on day 1. Grade 4 thrombocytopenia occurred in 16%, with only 3% of patients requiring platelet transfusion.[6]

It is important to point out that regardless of incidence, thrombocytopenia associated with gemcitabine and cisplatin regimens in these studies rarely resulted in bleeding and was, therefore, of little clinical significance. Nevertheless, this observed difference in thrombocytopenia between 28- and 21-day schedules of gemcitabine/cisplatin appears to be particularly cogent when considering
development of combinations of gemcitabine with carboplatin.

**Gemcitabine and Carboplatin**

Although there have been few direct comparisons of cisplatin- and carboplatin (Paraplatin)-containing regimens in non-small-cell lung cancer, available literature suggests that carboplatin is equally efficacious. For example, in a European Organization for Research and Treatment of Cancer (EORTC) trial reported by Klastersky et al, etoposide plus carboplatin resulted in survival equivalent to etoposide plus cisplatin in the treatment of advanced non-small-cell lung cancer.[7]

While early studies dosed carboplatin by body surface area, more recent trials have administered carboplatin based on formulas derived from a targeted area under the concentration-time curve (AUC), thus accounting for differences in renal excretion. Although carboplatin offers an improved therapeutic index, namely reduced nonhematologic toxicities, compared with cisplatin, additive myelotoxicity may be problematic when combining carboplatin with other myelosuppressive chemotherapeutic agents. In initial trials combining a day 1, 8, and 15 schedule of gemcitabine with carboplatin, severe thrombocytopenia was problematic, prompting some investigators to conclude that this regimen was not feasible.[8]

More recently, alternative dose schedules have been employed. One approach has been a 21-day schedule, with carboplatin administered on day 1 and gemcitabine on days 1 and 8. The rationale is that in 28-day schedules combining gemcitabine with either cisplatin or carboplatin, thrombocytopenia requires that the day-15 gemcitabine dose be omitted in over 50% of courses.

A recent trial by the Spanish Lung Cancer Group reported by Carrato et al[9] is particularly instructive in optimizing the dose and schedule of gemcitabine/platinum combinations. Patients with advanced non-small-cell lung cancer were treated with gemcitabine at 1,000 mg/m² and carboplatin, at an AUC of 5 mg/mL/min. In sequential cohorts of patients, gemcitabine was administered either on days 1, 8, and 15 of a 28-day cycle or on days 1 and 8 of a 21-day cycle. While these two schedules proved to be equally efficacious, hematologic toxicity, especially severe thrombocytopenia, occurred much more frequently with the 28-day cycle (61% vs 17%) (Table 2). This difference in toxicity was observed despite achieving a greater delivered dose intensity with the 21-day cycle.

Similarly, a pilot study of sequential combination chemotherapy by Edelman et al[10] at the University of California, Davis, used a 21-day schedule with day 1 and 8 dosing of gemcitabine at 1,000 mg/m² and carboplatin at an AUC of 5.5 for three cycles prior to sequencing to single-agent paclitaxel. The gemcitabine/carboplatin regimen was well tolerated, with nadir thrombocytopenia occurring on day 15, a nontreatment day, and with recovery by day 21 in the vast majority of patients (Figure 1).

Grade 4 thrombocytopenia was observed in 19% of patients, without significant bleeding sequelae. This level of thrombocytopenia is comparable to that seen in the 21-day regimens of gemcitabine/cisplatin[6] and gemcitabine/carboplatin.[9] The overall response rate in the Edelman study was 31% (95% confidence interval [CI] = 13%-53%) and the median survival was 10 months.[10] Table 3 compares the level of grade 4 thrombocytopenia observed in several studies investigating gemcitabine and carboplatin combinations. Based on relative efficacy and toxicity, new trials investigating gemcitabine/platinum combinations employing either cisplatin or carboplatin are using 21-day schedules with gemcitabine dosing on days 1 and 8.

Figure 2 shows the study design for a recently completed randomized phase II Southwest Oncology Group (SWOG) study (S9806) evaluating two different sequential combination chemotherapy regimens in advanced non-small-cell lung cancer. If the results prove to be encouraging, S9806 will provide the rationale for testing sequential vs concurrent three-drug combinations, with the objective of determining the relative therapeutic index of each approach.

To further evaluate the day-21 gemcitabine/carboplatin regimen developed by Edelman et al,[10] a National Coalition Trial will directly compare this regimen to paclitaxel/carboplatin and to the
nonplatinum combination of gemcitabine/paclitaxel (Figure 3). A proposed Cancer and Leukemia Group B (CALGB) trial will compare the sequential regimen of gemcitabine/carboplatin followed by weekly paclitaxel immediately to gemcitabine/carboplatin followed by weekly paclitaxel at the time of progressive disease, to the "triplet" of the three agents given concurrently (Figure 4).

Gemcitabine and Oxaliplatin

Oxaliplatin is a novel platinum derivative with a 1,2-diaminocyclohexane (DACH) carrier ligand, providing several therapeutic advantages over classic platinum compounds such as cisplatin and carboplatin. Oxaliplatin appears to be more potent than cisplatin, requires fewer DNA adducts to achieve equal levels of cytotoxicity, and is relatively non-cross-resistant.[12] Oxaliplatin has demonstrated impressive clinical activity against a number of tumor types, including malignancies where cisplatin has relatively little activity, such as colorectal cancer.

In non-small-cell lung cancer, the initial phase II trial has reported a 15% response rate.[13] Due to the unique synergism between gemcitabine and platinum compounds, combinations of oxaliplatin and gemcitabine are of particular interest. Based on proposed molecular mechanisms of interaction, the substitution of oxaliplatin for cisplatin or carboplatin may optimize cytotoxicity when combined with gemcitabine. Two phase I trials of this combination have been reported.[14]

The California Cancer Consortium is further evaluating this combination with a fixed dose of oxaliplatin at 130 mg/m2 on day 1 and escalating doses of gemcitabine on days 1 and 8 of a 21-day cycle (Table 4). Laboratory correlative studies performed on patient tumor tissue are designed to dissect potential molecular mechanisms of interaction, and include DNA repair genes (ERCC1 and ribonucleotide reductase), deoxycitadine deaminase, HER2/neu, apoptosis-related genes, and quantitation of oxaliplatin-DNA adducts in peripheral blood mononuclear cells. A subsequent phase II trial of this combination in advanced non-small-cell lung cancer is planned by the Southwest Oncology Group.

Summary

Gemcitabine/cisplatin has proven to be one of the most efficacious new combination chemotherapy regimens available for the treatment of non-small-cell lung cancer. The platinum derivatives carboplatin and oxaliplatin offer potential therapeutic advantages in terms of reduced toxicities or possible increased efficacy. Further studies of gemcitabine in combination with platinum derivatives are clearly warranted.

References:


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