Paclitaxel Plus Carboplatin in Advanced Non-Small-Cell Lung Cancer

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Despite a response rate of only 9%, single-agent carboplatin (Paraplatin) produced the best 1-year survival rate with the lowest toxicity in a five-arm Eastern Cooperative Oncology Group study of cisplatin (Platinol)

Introduction

Although lung cancer is not the most common cancer, it is still the leading cause of cancer death in men throughout the world, accounting for 29% of all cancer deaths in men in the European Community countries. The corresponding figure for women is 9%.[1,2] Closer to our home in Spain, data from the Tarragona Cancer Registry and the Catalonia Mortality Registry indicate that one in 14 men will develop lung cancer and nearly all of them will die of the disease.[3] However, survival time can be improved. A meta-analysis of cisplatin (Platinol)-based chemotherapy showed an increase of 1.5 months in median survival, with a 10% absolute increase of survival at 1 year.[4]

A recent randomized trial indicates that the addition of paclitaxel (Taxol) to cisplatin may lead to an additional 2-month improvement in survival.[5] Interestingly, single-agent paclitaxel has attained a promising median survival time of 40 weeks in patients with advanced non–small-cell lung cancer.[6] Prompted by the promising activity of paclitaxel, several groups are currently testing paclitaxel combinations to find the best chemotherapy regimen.

Logically, the first step is to combine paclitaxel with a platinum compound—they are cisplatin or carboplatin (Paraplatin). The rationale for combining paclitaxel with carboplatin stems from the five-arm Eastern Cooperative Oncology Group (ECOG) study in which 400 mg/m² of single-agent carboplatin, followed by mitomycin (Mutamycin), vinblastine (Velban), and cisplatin at the time of progression produced the best median survival (31.7 weeks) despite a 9% objective response rate. In addition, single-agent carboplatin turned out to be much less nephrotoxic and neurotoxic than the cisplatin combinations.[7] The European Lung Cancer Working Party study also showed that toxicity with a carboplatin/etoposide combination was significantly less than with a cisplatin/etoposide combination, although there were no differences in response rate or survival between the two arms.[8]

It can also be speculated that certain paclitaxel multigent combinations may potentially overcome drug resistance, and that paclitaxel cytotoxicity may increase with prolonged exposure duration.[9] For instance, recently, a unique resistance mechanism linked to molecular alterations in microtubules has been described in paclitaxel-resistant human ovarian cancer cells.[10] Likewise, automatic DNA sequencing has been used to detect β-tubulin point mutations in five of 49 (10%) tumors of non–small-cell lung cancer patients who were treated with single-agent paclitaxel.[11] None of those five patients whose tumors contained β-tubulin mutations obtained an objective response, whereas 12 of the remaining 44 patients without tubulin mutation (27%) had a partial or complete response. Moreover, median survival for patients without tubulin mutation was 8 months, with 1-year, 3-year, and 5-year survival rates of 22%, 10%, and 5%, respectively. In contrast, the median survival was only 2 months for the subset of patients with tubulin mutations (P = .029). Recently, the paclitaxel/carboplatin combination for advanced non–small-cell lung cancer has been the focus of several phase II trials in Europe. Extensive experience has been reported by Greek,[12,13] Dutch,[14] and Italian[15] investigators. These and other investigated studies[16-19] are reviewed here (Table 1). Although only four of these studies have been fully reported, results are encouraging.

Paclitaxel/Carboplatin Combination Studies

The Two Greek Phase II Studies
The first Greek study was a paclitaxel/carboplatin trial in previously untreated patients with locally advanced or metastatic (inoperable stage IIIA, IIIB, or IV) non–small-cell lung cancer. The primary objective was to assess response rate. The secondary objectives were to examine survival, time to progression, and toxicity. Patients received 175 mg/m² of paclitaxel by 3-hour infusion and carboplatin at an area under the concentration-time curve of 7 (AUC in mg/mL · min) in each 21-day cycle. Grade 3 neutropenia occurred in 7% of the patients, and grades 3 and 4 thrombocytopenia were observed in only 2%. Results have been published elsewhere.[12]

Inclusion criteria limited entry into the trial to chemotherapy-naive patients with histologically confirmed inoperable stage IIIA, IIIB, or IV non–small-cell lung cancer. All participants were required to have an ECOG performance status equal to or lower than 2, adequate hematological function (white blood cell count > 4.0 × 10⁹/L and platelet count > 100 × 10⁹/L), and an estimated life expectancy of more than 12 weeks. All patients gave their informed consent. Sixty patients were entered: 56 were male and four female; median age was 57; six patients were stage IIIA (10%), 20 patients were stage IIIB (33.3%), and 34 patients were stage IV (56.7%). This study found a 27.3% overall tumor response rate, progression-free survival of 6.85 months, and a median survival of 8.95 months with a 21.6% 1-year survival probability.

Based on the safety profile of paclitaxel/carboplatin, Kosmidis et al.[13] carried out a randomized study of two dose levels of paclitaxel plus a fixed dose of carboplatin in previously untreated patients with locally advanced or metastatic non–small-cell lung cancer. The primary objective of this study was to compare the objective response rate of patients treated with one of two doses of paclitaxel. The secondary aims were to compare time to disease progression, survival, toxicity, and quality of life. Patients were randomized to receive either 175 mg/m² or 225 mg/m² of paclitaxel (3-hour infusion) plus a fixed dose of carboplatin at an AUC of 6 in each 21-day cycle.

Ninety-nine patients were randomized to paclitaxel at 175 mg/m² (Group A) and 99 to paclitaxel at 225 mg/m² (Group B). The response rate among 90 evaluable patients in Group A was 25.6% (6 CR, 17 PR), whereas in Group B, the response rate among 88 evaluable patients was 31.8% (3 CR, 25 PR) (P = .733). Median time to progression favored the high-dose paclitaxel arm (4.3 months vs 6.4 months, P = .044). The median survival was 9.5 months for Group A vs 11.4 months for Group B (P = .16). The 1-year survival was 37% for Group A and 44% for Group B (P = .35). With a relative dose intensity of P = .94 in both groups, neurotoxicity (P = .025) and leukopenia (P = .038) were more pronounced in the high-dose paclitaxel arm. No toxic death was noticed. The authors concluded that higher dose paclitaxel prolongs the median time to progression but causes more neurotoxicity and leukopenia.[20]

**The Dutch Dose-Evaluation and Dose-Sequencing Phase I Study**

The background of this study derives from preclinical studies that had demonstrated a sequence-dependent cytotoxic effect for the cisplatin/paclitaxel combination in vitro. The paclitaxel/cisplatin sequence was shown to be more cytotoxic than the reverse sequence. Other sequence-dependent interactions had been reported for paclitaxel combined with doxorubicin (Adriamycin), cyclophosphamide, or etoposide.[21] Hence, the primary objective of this phase I trial was to evaluate a potential sequence-dependent interaction between paclitaxel and carboplatin. Secondary objectives were to examine survival, response rate, and toxicity. Six patients were allocated to each dose level and randomized to receive either paclitaxel followed by carboplatin or carboplatin followed by paclitaxel. The original dose levels were 100 mg/m² of paclitaxel and 300 mg/m² of carboplatin every 28 days.

Inclusion criteria limited entry into the trial to chemotherapy-naive patients with histologically confirmed stage IIIB or IV non–small-cell lung cancer. All participants were required to have an ECOG performance status less than or equal to 2, adequate hematological function (absolute granulocyte count > 2.5 × 10⁹/L, platelet count > 100 × 10⁹/L), and an estimated life expectancy of more than 12 weeks. All patients gave their informed consent. Sixty patients were entered: 56 were male and four female; median age was 57; six patients were stage IIIA (10%), 20 patients were stage IIIB (33.3%), and 34 patients were stage IV (56.7%). This study found an overall response rate of 11% (three complete responses and two partial responses) with a 6-month median survival time and 11% (three complete responses and two partial responses) with a 1-year survival probability. When the response rate was broken down by paclitaxel dose with a cutoff level of 175 mg/m², a higher objective response rate was observed with paclitaxel doses above this level.

From this Dutch study,[14] we can draw five conclusions. First, a 28-day paclitaxel/carboplatin cycle induces a higher response rate and survival as a function of the paclitaxel dose. Second, a minimum paclitaxel dose (175 mg/m²) in a 3-hour infusion is required for activity in advanced non–small-cell lung cancer. Third, no sequence-dependent toxicities or sequence-dependent pharmacokinetic interactions occur with a paclitaxel/carboplatin combination. Fourth, the paclitaxel/carboplatin
regimen is well tolerated (grade 4 neutropenia occurred in only 15% of the patients). Finally, less thrombocytopenia was observed with paclitaxel/carboplatin than with single-agent carboplatin.

The Italian Dose-Escalation Phase I/II Study
This trial, recently published by Scagliotti et al,[15] explored the efficacy of paclitaxel/carboplatin in advanced non-small-cell lung cancer. Paclitaxel was administered at doses ranging from 130 to 235 mg/m² by 3-hour infusion and carboplatin from 230 to 375 mg/m². The baseline disease characteristics of the 50 patients entered were as follows: 43 men and seven women; one patient was stage IIIA (2%), 31 patients were stage IIIB (62%), and 18 patients were stage IV (36%). Of the 50 patients enrolled, 47 were evaluable for response with a 38% objective tumor response (one complete response and 17 partial responses). Median survival was 13 months, and the 1-year survival rate was 49%.

When the investigators analyzed response by paclitaxel/carboplatin dose level, a 48% objective response rate was found with doses higher than 195 mg/m² for paclitaxel, and 350 mg/m² for carboplatin, whereas the response rate dropped to 27% with lower doses (< 195 mg/m² and 350 mg/m²). In summary, this phase I/II Italian study confirmed the efficacy of paclitaxel/carboplatin chemotherapy in advanced non-small-cell lung cancer and may indicate a dose-response relationship. Toxicity was acceptable with no severe thrombocytopenia; grade 3/4 neutropenia was observed in 36% of all cycles. In comparison, a recent North American study[22] found that for the short-infusion paclitaxel/carboplatin regimen, the recommended doses are 175 to 225 mg/m² of paclitaxel and 400 mg/m² of carboplatin (or, if the Calvert formula is used to calculate the dose, an AUC of 6 or 7 should be used).

Other Paclitaxel/Carboplatin Regimens
Other phase I/II studies of short-infusion paclitaxel/carboplatin regimens have been published in abstract form[16-19] using 100 to 250 mg/m² paclitaxel doses and 150 to 500 mg/m² carboplatin doses yielding objective response rates of 24% to 52% (Table 1). Based on these results, it seemed quite clear that the next step was to compare the activity of paclitaxel/carboplatin with that of paclitaxel/cisplatin, because although both cisplatin and carboplatin are active drugs, carboplatin produces less toxicity. A large European study was designed to compare the two paclitaxel/platinum combinations.

Paclitaxel/Carboplatin vs Paclitaxel/Cisplatin in Advanced NSCLC
This multicenter study involved 16 countries in Europe. The design of the study is reported here. From April 1996 to July 1997, 618 untreated patients with advanced non-small-cell lung cancer were randomized to receive paclitaxel/carboplatin or paclitaxel/cisplatin. The primary objective of this phase III trial was to compare the response rates and safety profiles of the two combinations. Secondary objectives were to compare survival and effects on patient quality of life as measured by a subscale derived from the European Organization for Research and Treatment of Cancer QLQ-C30-LC13 questionnaire.

Randomization was stratified by four factors: performance status, disease stage, histology, and investigation center. Paclitaxel at a dose of 200 mg/m² was administered by a 3-hour infusion followed by either carboplatin at an AUC of 6 by 30-minute infusion or cisplatin at 80 mg/m² by 1-hour infusion in a 21-day cycle.

Inclusion criteria were similar to the other randomized trials and included chemotherapy-naive patients with histologically confirmed stage IIIB or IV non-small-cell lung cancer. All participants were required to have at least one measurable lesion (with a diameter equal to or greater than 2 × 2 cm on imaging), which had to be outside of a previous radiotherapy field. An ECOG performance status of 0 to 2 or a Karnofsky performance status equal to or greater than 60 was also required. All patients gave their signed informed consent. The preliminary results of 289 patients were presented at the 1998 meeting of the American Society of Clinical Oncology.

Data were available on 287 pts. Characteristics of these patients included: performance status of 0/1 in 81% and 2 in 19%; stage IIIB disease in 31% and stage IV in 69%; squamous cell carcinoma, 33%; non-squamous, 67%. The median age of patients was 57 years (range, 29 to 79); 81% were male; 35% had a weight loss of more than 5%; 55% had 2 or more lesions. Safety data on 1,211 courses (283 pts), with a median of 4 courses (range, 1 to 10) showed 32% grade III/IV neutropenia, 2% grade III/IV thrombopenia, 9% grade III/IV arthralgia/myalgia, 27% grade II/III peripheral neuropathy, 27% grade II/III asthenia, and 10% grade III/IV nausea/vomiting. The authors concluded this (618 pts) trial allows comparing cisplatin with carboplatin in combination with paclitaxel. The interim results showed no unexpected toxicity nor any large response rate difference. Further follow-up is
Summary

What conclusions can be drawn from these phase I/II trials? The first results of these European pilot trials provide evidence that a paclitaxel/carboplatin regimen has acceptable toxicity and produces a high response rate in patients with advanced or metastatic non–small-cell lung cancer. However, a proviso should be kept in mind: the optimal duration of paclitaxel administration has not yet been determined, and in the North American studies, higher response rates were observed when paclitaxel was administered by 24-hour infusion as opposed to a 3-hour infusion when combined with carboplatin.[24,25] For comparison, Table 2 includes the three European studies and the two North American studies.

In conclusion, the four European studies discussed here demonstrated that 1) a higher response rate and a longer median survival is attained with the paclitaxel/carboplatin regimen in a 21-day cycle than when using a 28-day cycle; 2) the toxicity profile of the 21-day cycle is mild, with a platelet-sparing effect; 3) the lowest effective paclitaxel dose is 175 mg/m² when administered by 3-hour infusion; 4) as opposed to classical cisplatin combinations, a paclitaxel/carboplatin regimen in a 21-day cycle requires no ancillary measures (blood product transfusions, antiemetic therapy, or hospitalization for neutropenic fever); and 5) in our experience, tubulin gene mutations could be a possible specific marker of paclitaxel resistance.

These findings indicate that the paclitaxel/carboplatin regimen should be considered for other large-scale clinical trials taking into account different paclitaxel schedules (weekly vs every 3 weeks) or infusion times (3 hours vs 24 hours).

References:


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