Paclitaxel in the Treatment of Small-Cell Lung Cancer

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New treatment strategies for small-cell lung cancer patients are required, as there have been few developments in the past 20 years. Paclitaxel (Taxol) has been shown to be effective in non-small-cell lung cancer when given in

Introduction

Little progress has been made in the treatment of small-cell lung cancer during the past 2 decades. Patients without distant metastases currently have a 10% to 15% chance of survival at 5 years, and with the optimization of chemotherapy protocols and the introduction of multimodality treatments, prognosis in this subgroup of patients has been improved in recent years. Nevertheless, the prognosis of patients with distant metastases remains poor, with a 3-year survival rate of less than 5% and nearly no chance of cure.

Furthermore, in patients with extensive disease, no improvement of treatment results has been observed in the past 25 years. Recently, the Copenhagen Group[1] published an analysis of the prognosis of patients with extensive disease treated from 1973 to 1981 compared to the prognosis of patients treated from 1982 to 1992. The median survival of 508 patients treated in the former studies was 208 days. These results were not significantly inferior to the median survival of 215 days for 423 patients treated in the more recent trials. Our study group at University Hospital in Marburg, Germany has obtained similar results. From 1981 to 1993, we performed five randomized trials including 738 patients with metastatic disease. The median survival of the whole group was 234 days, and the survival curves of these five consecutive trials were nearly identical. From the results of these trials, it appears that so-called standard chemotherapy regimens show a comparable activity[1]at least in the subgroup of patients with extensive small-cell lung cancer[1]and no particular drug combination seems to be superior to others. To overcome this stagnation of treatment results in small-cell lung cancer, the introduction of new drugs with a higher activity into treatment protocols is necessary.

Paclitaxel (Taxol) is a relatively new cytostatic drug with a unique mechanism of action. The drug is highly active in various malignancies such as ovarian cancer, breast cancer, and non-small-cell lung cancer. This well-documented activity, even in tumors resistant to standard chemotherapy regimens, makes the drug especially interesting for testing in small-cell lung cancer.

Single-Agent Paclitaxel

Two trials in patients with metastatic small-cell lung cancer have tested the activity of paclitaxel as single-agent treatment. In the Eastern Cooperative Oncology Group (ECOG) study from Ettinger et al,[2] 32 patients received a dose of 250 mg/m² as a 24-hour infusion every 3 weeks. The remission rate was 34%, and median survival was 43 weeks. In the second trial from the North Central Cancer Treatment Group (NCCTG),[3] 37 patients were treated with a similar protocol; 41% of them achieved a partial remission. These small phase II trials demonstrated the activity of paclitaxel for the treatment of small-cell lung cancer and provided the basis for the subsequent incorporation of this drug into polychemotherapy regimens. To date, experience with paclitaxel in combination chemotherapy for small-cell lung cancer is still limited. Table 1 gives an overview of the currently available data, including the number of evaluable patients with limited or extensive disease in each study.

Cisplatin/Paclitaxel in Extensive Disease

The combination of cisplatin (Platinol) and paclitaxel has been tested in two phase II trials—one from the NCCTG and one from Marburg University.

The NCCTG Trial
In the study from the NCCTG,[4] 71 chemotherapy-naive patients with extensive disease were treated with cisplatin and paclitaxel. At dose level 1, 23 patients received a dose of cisplatin (75 mg/m² on day 1) and paclitaxel (135 mg/m² on day 1). Due to the very low toxicity with no World Health Organization (WHO) grade 3 or 4 hematologic toxicity, 48 patients received an increased paclitaxel dose of 175 mg/m² on day 1. A total of six cycles were given in 3-week intervals. The treatment schedule is given in Table 2.

At the higher dose level, leukopenia WHO grade 3 was seen in 24% and WHO grade 4 leukopenia in 2% of the patients. No severe thrombocytopenia occurred. Other severe clinical side effects were nausea in 18%, vomiting in 13%, myalgia in 4%, and neurotoxicity in 2%.

The response to treatment was 71% at the low dose and 89% at the high dose. Progression-free survival (4.8 vs 5.5 months) as well as median survival (7.9 vs 8.7 months) were slightly higher in patients receiving the higher paclitaxel dose.

German Multicenter Trials

In the multicenter German study conducted at Marburg University, the combination of cisplatin (75 mg/m² on day 1) and paclitaxel (175 mg/m² on day 1) was administered to 62 patients with metastatic small-cell lung cancer. Six cycles were given in 3-week intervals to 49 male patients and 13 female patients. Median performance status was WHO grade 1, and the median age was 62 years. An elevated lactate dehydrogenase (LDH) level was documented in 36 patients (56%). (The main patient characteristics are summarized in Table 3.) All of the patients had metastatic organ involvement, 25 patients (40%) had one involved site, 22 patients (35%) had two metastatic sites, and 15 patients (24%) had three or more metastatic sites.

At least five cycles of chemotherapy were given to 33 patients (53%). Fifteen patients received only one or two cycles, and another 15 patients only three or four cycles. Treatment was stopped prematurely because of progressive disease in 21 patients and death during the induction therapy in three patients. In four additional cases, patients refused further treatment, and in two patients, renal impairment was responsible for the discontinuation of the chemotherapy. Additional severe clinical side effects were the occurrence of WHO grade 3 myalgia in two patients. Despite these side effects, treatment was well tolerated overall. Regarding hematologic toxicity, thrombocytopenia was observed in only two cycles (WHO grade 3) and leukopenia in only one cycle (WHO grade 3).

The treatment results of the Marburg and NCCTG trials are summarized in Table 4. Eight patients (13%) achieved a complete remission and 35 patients (56%) a partial remission, for an overall response rate of 69%. No change was seen in 11 cases, and eight patients had progressive disease despite therapy. The median progression-free survival of all patients was 156 days, and the median survival 356 days. Figure 1 shows the survival curve for all patients.

Both trials indicate that the combination of cisplatin (75 mg/m² on day 1) and paclitaxel (175 mg/m² on day 1) as a 3-hour infusion is a well-tolerated regimen in patients with small-cell lung cancer, with mild hematologic side effects. Therefore, the addition of the third drug seems to be feasible in order to achieve a further intensification of the treatment.

Three-Drug Combinations

Three-drug combinations including paclitaxel have been tested in three different trials. While the study at the M. D. Anderson Cancer Center[5] added intravenous etoposide (now available generically) to the drug combination cisplatin/paclitaxel, the trials from The Sarah Cannon Cancer Center[6] and the Hamburg-Grosshansdorf Hospital[7] used prolonged oral etoposide with a carboplatin (Paraplatin)/paclitaxel combination. The different treatment protocols are summarized in Table 5.

The M. D. Anderson Trial

A total of 30 patients who did not receive prior chemotherapy were included in the study from M. D. Anderson. The investigators intended to perform a dose escalation of paclitaxel and started with a paclitaxel dose of 130 mg/m² on day 1 together with cisplatin at 75 mg/m² on day 2, and etoposide at 80 mg/m² on days 2 through 4. Even at this starting dose, substantial hematologic and clinical toxicities precluded further dose increases.

In 48% of all cycles WHO grade 4 neutropenia was observed. In 6% of all cycles, neutropenic fever occurred, and one patient died due to a septic complication. Furthermore, the investigators observed the development of a fatigue/malaise syndrome (WHO grade 2 to 3) in one-third of all patients. Despite this relatively high toxicity, the treatment induced at least a partial remission in all but one patient. The complete remission rate was 10%. For all patients, the median progression-free survival
was 7.6 months, and the median survival was 14.3 months.

**The Sarah Cannon Cancer Center Trial**

A total of 117 patients were included in the study from the Sarah Cannon Cancer Center.[6] Of these 117 patients, 61 had extensive disease and 56 had limited disease. After 38 patients received the first dose level (paclitaxel at 135 mg/m² as a 1-hour infusion on day 1, together with carboplatin at a target area under the concentration-time curve of 5 [AUC in mg/mL - min], and etoposide at 75 mg po for 10 days), subsequent patients received a higher dose (paclitaxel at 200 mg/m², and carboplatin at an AUC of 6). The treatment schedule is shown in Table 5. The side effects of both dose levels are summarized in Table 6. Based on all treatment courses, WHO grade 4 leukopenia was seen in 8% at the lower dose, and 38% at the higher dose. The incidence of WHO grade 3 or 4 thrombocytopenia was relatively low, with 4% at the low dose, and 8% at the high dose. About 10% of the patients had neutropenic fever. Compared to the M. D. Anderson trial using cisplatin, a smaller proportion of patients receiving the high-dose regimen suffered from fatigue/malaise syndrome (10% vs 33%).

**Activity in Extensive Disease**

For patients with extensive disease, the prognostic factors among patients assigned to both dose levels were comparable. At the low-dose level, 14 men and 9 women were included, compared to 19 men and 19 women at the high-dose level. Half of all patients had an elevated LDH serum level, with no difference between the two groups. Also, the number of metastatic sites was well balanced, with 56% vs 50% showing one metastatic site, 30% vs 42% showing two metastatic sites, and 14% vs 8% showing three metastatic sites in the low- and high-dose arms, respectively. However, a higher proportion of patients in the high-dose arm had an ECOG performance status of 0 to 1 (46% vs 82%). The overall treatment results demonstrated improved efficacy with the increased doses of paclitaxel and carboplatin. Similarly, the analysis of survival showed a statistically significant advantage for the high-dose arm, with a median survival of 7 vs 10 months. These treatment efficacy data are summarized in Table 7, and the survival curves for both dose levels in extensive disease are shown in Figure 2.

**Activity in Limited Disease**

Patients with limited disease received an additional thoracic radiotherapy dose of 45 Gy during the third and fourth cycles of chemotherapy. This concurrent use of chemotherapy and radiotherapy was associated with WHO grade 3 esophagitis in 20% of patients. In two cases, grade 4 esophagitis was noticed. In terms of hematologic toxicity, the concurrent dose of chemotherapy with thoracic radiotherapy was feasible. Known prognostic factors were similar in the two dosage arms. As in patients with extensive disease, the higher paclitaxel and carboplatin doses resulted in increased response rates. The complete remission rate was 40% in the low-dose arm, compared to 71% in the high-dose arm, and the overall response rate was 93% vs 98% in the low- and high-dose arms, respectively. The median follow-up of these patients is still too short to assess whether the higher response rate will also result in a prolongation of survival. There is no difference in survival between the two dosage arms at 1 year after treatment. The median survival of all patients is currently greater than 16 months.

**The Hamburg-Grosshansdorf Trial**

A study from Hamburg-Grosshansdorf included 89 patients with limited disease (69 were men and 20 women). The median age was 61 years, and these patients received a similar treatment protocol to the patients in The Sarah Cannon Cancer Center trial. Paclitaxel was given at a dose of 175 mg/m² on day 1, carboplatin at an AUC of 5, and etoposide at an oral dose of 100 mg/day on days 2 through 8. Hematologic toxicity was less pronounced in this trial than it was in the high-dose arm of the Sarah Cannon trial. WHO grade 4 leukopenia was observed in 24% of all patients, and WHO grade 3 or 4 thrombocytopenia was seen in 5%. The incidence of neutropenic fever was 3%. The response rates in the trial from Hamburg showed a complete remission rate of 38% and an overall response rate of 91%. An analysis of survival has not yet been performed due to the short follow-up period.

**Discussion**

The experience with paclitaxel in the treatment of small-cell lung cancer is still limited. Until now there have been only a few trials with mature treatment results available. In two of these trials, the combination of cisplatin and paclitaxel was used. A trial from the NCTG and a multicenter German trial conducted by Marburg University each demonstrated that this two-drug regimen is highly active.
in extensive small-cell lung cancer and at least as active as standard regimens. Both trials used paclitaxel (175 m/m²) plus cisplatin (75 mg/m² on day 1), and noticed only mild to moderate hematologic and clinical toxicities. The response rates ranged from 70% to 90%, and median progression-free survival in both trials was about 5.5 months. Median survival was approximately 9 months in the NCCTG trial, and 12 months in the Marburg trial. Because of the long median survival time in the Marburg trial, a matched-pair analysis was performed to compare the survival of patients treated with the cisplatin/paclitaxel protocol to a patient population with identical prognostic factors treated with so-called standard regimens like cyclophosphamide (Cytoxan)/doxorubicin (Adriamycin)/vincristine or cisplatin/etoposide in previous trials. In this matched-pair analysis, the prognostic factors (ie, LDH, number of distant metastases, gender, and performance status) were taken into consideration. The distribution of these prognostic factors in both patient populations is shown in Table 8.

The comparison of survival curves demonstrated a statistically significant superiority of the paclitaxel/cisplatin-treated patients in comparison to the historical control group (Figure 3). This is remarkable, since, in all of the previously performed trials in patients with extensive small-cell lung cancer, we have been unable to demonstrate the superiority of one drug combination over others. Nevertheless, this matched-pair analysis with historical controls cannot be used to establish the superiority of this new drug combination. Historical comparisons may be biased by the selection of patients with prognostic factors that are not recognized as “typical” patient characteristics and by the fact that progress in treatment and supportive care has been made over time. This matched-pair analysis does, however, provide the basis for a randomized trial comparing the cisplatin/paclitaxel regimen to a standard protocol.

The mild hematologic toxicity of the two-drug combination of paclitaxel and cisplatin allows the addition of a third drug in order to achieve further treatment intensification. Three trials have been performed using three-drug combinations.

In the trial at the M. D. Anderson Cancer Center, the maximum tolerated dose of paclitaxel given together with cisplatin (75 mg/m²) and etoposide (80 mg/m² for 3 days) was found to be 130 mg/m². At this dose level, the investigators observed substantial hematologic and clinical toxicity, with fatigue/malaise syndrome in one-third of the patients. In combination with carboplatin (AUC of 5) and oral etoposide (75 mg/day for 10 days), a paclitaxel dose of 175 to 200 mg/m² seemed to be tolerable.

The increase of the paclitaxel and carboplatin doses in the trial at The Sarah Cannon Cancer Center resulted in a significant improvement in survival among patients with extensive small-cell lung cancer, prolonging median survival from 7 to 10 months. This result points to a dose-response relationship for paclitaxel in small-cell lung cancer. However, it cannot be concluded that the addition of etoposide to the cisplatin/paclitaxel combination improves survival. Randomized trials have been initiated to determine whether the incorporation of paclitaxel to standard treatment regimens will result in a substantial improvement in the outcome of patients with small-cell lung cancer. Investigators at The Sarah Cannon Cancer Center have started a randomized trial comparing carboplatin/etoposide to carboplatin/etoposide/paclitaxel, and researchers at the Hamburg-Grosshansdorf Hospital have initiated a multicenter trial comparing carboplatin/etoposide/vincristine to carboplatin/etoposide/paclitaxel. Both trials will include patients with limited disease as well as those with extensive disease.

References:


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