Cancer Chemother Pharmacol (1990) 26: 369–372

Cancer Chemotherapy and Pharmacology

Phase II study of carboplatin in untreated, inoperable non-small-cell lung cancer

Ulrich Gatzemeier[1], Marlene Heckmayr[1], Dieter Klaus Hossfeld[2], Reinhart Zschaber[2], Wolf Achterrath[3], and Luigi Lenaz[3]

[1] Department of Thoracic Oncology, Grosshansdorf Hospital, Grosshansdorf, Federal Republic of Germany
[2] Department of Hematology and Oncology, University Hospital, Hamburg, Federal Republic of Germany
[3] Bristol-Myers Squibb Company, New York, NY 10154, USA

Received 28 August 1989/Accepted 9 March 1990

Summary. A total of 51 previously untreated patients with non-small-cell lung cancer (NSCLC) were treated with 130 mg/m^2 carboplatin given every 4 weeks as an i.v. infusion on days 1, 3, and 5. Ten patients achieved a partial response and five, a minor response. The overall response rate was 20% (95% confidence limits, 8%–32%). The median duration of response was 3 months and the median overall survival was 4.5 months. Leucopenia, thrombocytopenia and anemia of WHO grade 3 occurred in 4%–6% of patients and grade 3 nausea and vomiting was observed in 8% of our subjects. Grade 4 thrombocytopenia occurred in 3 (6%) patients. Apart from nausea and vomiting, nonhematologic toxicities above grade 2 were not observed. Further trials using carboplatin in NSCLC as a single agent or in combination with other chemotherapeutic agents or radiation are warranted.

Introduction

Cisplatin-containing regimens, especially in combination with etoposide or vindesine and/or mitomycin C, have demonstrated antineoplastic activity in non-small-cell lung cancer (NSCLC) and are frequently used in the treatment of this disease [11, 13, 15, 17, 18, 20, 29, 31]. Treatment with cisplatin/etoposide and cisplatin/vindesine is limited mainly due to cisplatin's toxicity, namely, nausea and vomiting, ototoxicity, peripheral neuropathy and renal function disturbances [13, 18, 29]. Treatment with cisplatin/vindesine is additionally limited because of additive peripheral neurotoxicity [13, 15, 18, 29].

Carboplatin is a cisplatin analogue that may be active in NSCLC [8]. In two randomized studies [1, 34] it induced statistically significantly less nausea/vomiting, nephro- and ototoxicity and peripheral neuropathies than did cisplatin. In nude mice, the antineoplastic activity of carboplatin is schedule-dependent in several xenograft tumors [24, 25]; at the same total delivered dose, the antineoplastic activity was higher when the drug was given 3 days/week than with single weekly application [24, 25]. Based on this clinical and experimental background, we conducted a phase II study of carboplatin given every 4 weeks on days 1, 3, and 5 to patients with NSCLC.

Offprint requests to: Luigi Lenaz, Bristol-Myers Squibb Company, 345 Park Avenue, New York, NY 10154, USA

Patients and methods

Selection of patients. Eligibility criteria for this study included pathologically confirmed, inoperable NSCLC; an estimated survival of at least 3 months; a Karnofsky performance status of at least 50%; no prior chemo- or radiotherapy; no brain metastases; normal bone marrow (leucocytes, $\geq 4 \times 10^9$/l; platelets, $\geq 100 \times 10^9$/l), renal (serum creatinine, ≤ 1.5 mg/100 ml; creatinine clearance, ≥ 60 ml/min), liver (serum bilirubin, ≤ 2 mg/100 ml) and neurologic functions; and normal serum electrolyte values. All patients gave informed consent to their participation in this investigation.

Treatment plan. Patients were hospitalized during treatment. Chemotherapy consisted of 130 mg/m^2 carboplatin given on days 1, 3, and 5 as an i.v. infusion over 30 min without pre- or posthydration. No dose escalations were carried out. Low-dose antiemetics were given prophylactically. Cycles were to be repeated every 4 weeks if WBC and platelet values were $\geq 4 \times 10^9$/l, and $\geq 100 \times 10^9$/l, respectively, or were to be delayed until recovery to such values. Patients who either had progressive disease after the first cycle or any time thereafter or failed to achieve a complete (CR) or partial remission (PR) after the third cycle received no further treatment with carboplatin; their subsequent treatment was decided on an individual basis.

Pretreatment and follow-up studies. Baseline studies included complete physical examination, with measurement of all neoplastic lesions; X-ray and computerized tomography (CT) of the chest; CT and ultrasound of the abdomen; and CT of bone and brain. Bone lesions were measured by roentgenography. The size of neoplastic lesions was determined before treatment, before each cycle, 4 weeks after the last course and then every 3 months. A complete hemogram, serum creatinine and creatinine clearance values, serum electrolyte levels and liver function values were obtained before treatment, before each cycle and 4 weeks after the last cycle. During chemotherapy, complete blood counts were monitored

Table 1. Patients' characteristics

Patients (*n*)	51
Men/women	42/9
Age (years):	
Median	59
Range	36–71
Karnofsky performance status (%):	
Median	80
Range	60–100
Number of patients with ≥80%	38
Number of patients with 60%–70%	13
Histology:	
Squamous-cell	29
Adenocarcinoma	11
Large-cell	9
Undifferentiated	2
Stage:	
Limited	3
Extensive	48

Table 2. The most severe toxicities observed in 51 patients receiving 103 courses of carboplatin

	WHO grade:				
Toxicity	0	1	2	3	4
Leucopenia	34 (67%)	10 (20%)	4 (8%)	3 (6%)	0
Thrombocytopenia	36 (71%)	7 (14%)	3 (6%)	2 (4%)	3 (6%)
Anemia	33 (65%)	10 (20%)	5 (10%)	3 (6%)	0
Serum bilirubin	51 (100%)	0	0	0	0
Transaminases (SGOT/SGPT)	42 (82%)	5 (10%)	4 (9%)	0	0
Fever	49 (96%)	2 (4%)	0	0	0
Alopecia	44 (86%)	2 (4%)	3 (6%)	2 (4%)	0
Nausea/vomiting	23 (45%)	20 (39%)	4 (8%)	4 (8%)	0

Values are expressed in numbers of patients; the corresponding percentages (of a total of 51 patients) are shown in parentheses

weekly. Qualitative assessment of nausea and vomiting was done by the nursing staff during the period of patient hospitalization.

Treatment response/toxicity. Patients were considered to be evaluable for response and toxicity if they had received at least one treatment cycle. Tumor response, response duration and toxicity were classified according to WHO criteria. The median duration of response and median survival were calculated by the Kaplan-Meier method. Survival was calculated from the 1st day of treatment.

Results

From July 1987 to July 1988, 52 consecutive patients entered the study. One patient was not evaluable because he refused treatment during the first course. Table 1 summarizes the clinical characteristics of all evaluable patients. In all, 3 patients had limited disease and 48 had extensive disease, mostly with extrathoracic metastases. A total of 51 patients received at least one course of carboplatin and were evaluable for response and toxicity; a total of 103 cycles were completed (median 2/patient; range, 1–4). On the dose schedule tested, carboplatin induced 10 (20%) partial remissions (95% confidence limits, 8%–32%). In all, 20 patients showed a minor response or no change and 21 had progressive disease; no CR was observed. PRs were seen in all cell types. The response rate for squamous-cell carcinoma was 24%, that for adenocarcinoma was 18% and that for large-cell cancer was 11%. Only two patients had undifferentiated carcinoma and showed no response. After a median observation period of 12 months, the median duration of response was 3 months. Median overall survival was 4.5 months; patients classified as PR or MR/NC had a median survival of 7 and 5 months, respectively. The median survival for patients with progressive disease was 2 months.

Patients with an initial Karnofsky performance status of ≥80% survived statistically significantly longer than did those with a lower performance status (5 vs 2 months; chi-square test, $P = 0.03$). In our study, the performance status of 38 patients was ≥80% and that of the remaining 13 was 60%–70%. No other prognostic factor (e.g., sex, age, cell type) affected median survival to a statistically significant degree. By cell type, the difference in median survival was not statistically significant, possibly because there were too few patients.

The most severe chemotherapy-related toxicities are outlined in Table 2. WHO grade 4 thrombocytopenia occurred in 6% of the patients; leucopenia, thrombocytopenia and anemia of WHO grade 3 occurred in 6%, 4% and 6% of our subjects, respectively. Recovery was always complete by day 28. Nausea/vomiting and alopecia of WHO grade 3 were seen in 8% and 4% of the patients, respectively. No other toxicities above WHO grade 2 occurred. Nephro- and ototoxicity and peripheral neuropathy were not observed.

Discussion

Cisplatin-containing regimens are often used for the treatment of NSCLC [11, 13, 15, 17, 18, 20, 29, 31]. However, the use of cisplatin is limited because of nausea/vomiting, nephro- and ototoxicity and peripheral neuropathies [13, 15, 18, 29]; furthermore, time-consuming hydration programs are necessary to avoid severe nephrotoxicity [13, 15, 18, 29]. The cisplatin analogue carboplatin can be given without hydration and, unlike cisplatin, it rarely induces severe non-hematologic toxic effects. We confirmed the good tolerance of carboplatin: nephrotoxicity, ototoxicity and peripheral neuropathy were not observed in this study. Vomiting was severe in only four patients, and approximately half of our subjects experienced no nausea or vomiting. No other severe non-hematologic toxicities were observed. The main hematologic side effect was thrombocytopenia, which was severe in 10% of our patients. No treatment delays were required, as recovery of blood

counts was always complete by day 28. It is noteworthy that approximately 2/3 of the patients experienced no bone marrow suppression, suggesting that provisions for dose escalation should have been made in the treatment plan.

This study shows that single-agent carboplatin, with an overall response rate of 20%, is effective in patients with advanced NSCLC and extrathoracic disease. Another non-randomized phase II study carried out by Olver et al. [28] reported no responses in 17 untreated and 18 previously irradiated patients. Three randomized studies, including a carboplatin single-agent arm in patients with either no prior treatment or prior radiotherapy only, were carried out by Kramer et al. [22], Kreisman et al. [23] and Bonomi et al. [7]. In these trials, carboplatin induced partial remission rates of 16%, 12% and 9% in 70, 50 and 88 patients, respectively [7, 22, 23]. Thus, of 294 patients treated in 5 studies, 35 responses were reported, for an overall response rate of 12% (range, 8–16%). Although no statistically significant differences were seen in this and other studies [7, 22, 23, 28], there is a consistent trend indicating higher response rates for squamous-cell (19 of 113 cases, or 17%) and large-cell carcinomas (9 of 54 patients or 17%) as compared with adenocarcinoma (7 of 131 subjects or 5%).

In the present study, carboplatin was given every 4 weeks on days 1, 3, and 5. In previous randomized studies [7, 22, 23], comparable doses of carboplatin were given as single-bolus injections every 4 weeks. Olver et al. [28] also used carboplatin at comparable doses, but on a daily × 5 schedule every 4 weeks. Thus, contrary to the preclinical data, no clear-cut trend suggesting a schedule dependency in favour of split doses emerged from the clinical trial, and the possible influence of the different schedules on the activity of carboplatin in NSCLC remains uncertain. Results of published studies show that carboplatin is probably an active agent in NSCLC. In disease-oriented phase II studies, it has induced overall response rates similar to those obtained with cisplatin and other agents more often used in NSCLC. In these trials, remission rates of 7%–35% were achieved with etoposide [2, 3, 6, 9, 14, 27, 32], those of 0–33% were obtained with cisplatin [11, 12, 16, 19, 21], rates of 0–29% were attained with ifosfamide [5, 10, 19, 26, 30], those of 0–30% were achieved with vindesine [19, 33] and rates of 9%–40% were obtained with mitomycin C [4]. Further evaluation of carboplatin as a single agent and as part of combination chemotherapy or combined modality approaches in NSCLC is warranted.

References

1. Adams M, Kerby IJ, Rocker I, Evans A, Johansen K, Franks CR (1987) Comparison of the toxicity and efficacy of cisplatin (CDDP) and carboplatin (JM8) in advanced ovarian cancer. Proceedings of the European Conference on Clinical Oncology, Madrid, 1–4 Nov.: 207
2. Anderson G, Payne H (1985) Response rate and toxicity of etoposide (VP-16) in squamous carcinoma of the lung: report from the Lung Cancer Treatment Study Group. Semin Oncol 12 [Suppl 2]: 21
3. Anderson G, Peel ET, Cheong CMB, Broderick NJ (1982) Etoposide – an effective single drug for treating bronchogenic carcinoma. Clin Oncol 8: 215
4. Bakowski MT, Crouch JC (1981) Chemotherapy of non-small cell lung cancer: a reappraisal and a look to the future. Cancer Treat Rev 10: 159
5. Banks J, Anderson EG, Smith AP (1989) Failure of response to ifosfamide in squamous cell bronchogenic carcinoma. Cancer Chemother Pharmacol 23: 128
6. Bauer G, Bremer K (1986) Sequentielle Therapie nichtkleinzelliger Bronchialkarzinome mit Etoposid und Cisplatin. Krebsmedizin 7: 10
7. Bonomi PD, Finkelstein DM, Ruckdeschel JC, Blum RH, Green MD, Mason B, Hahn R, Tormey DC, Harris J, Comis R, Glick J (1989) Combination chemotherapy versus single agents followed by combination chemotherapy in stage IV non small cell lung cancer: a study of the Eastern Cooperative Oncology Group. J Clin Oncol 7: 1602
8. Canetta R, Rozencweig M, Carter SK (1985) Carboplatin: the clinical spectrum to date. Cancer Treat Rev 12 [Suppl A]: 125
9. Chapman R, Itri L, Gralla R, Kelsen D, Caspar E, Golbey R (1982) Phase II trial of VP16-213 in non-small cell lung cancer (NSCLC). Cancer Chemother Pharmacol 7: 205
10. Costanzi JJ, Morgan LR, Hokanson J (1982) Ifosfamide in the treatment of extensive non-oat cell carcinoma of the lung. Semin Oncol 9 [Suppl 1]: 61
11. Crinó L, Darwish S, Corgna E, Meacci ML, Di Costanzo F, Buzzi F, Fornari G, Santi F, Ballatori E, Luccioli L, Santucci A, Davis S, Tonato M (1988) Treatment of advanced non-small cell lung cancer (NSCLC). The "Umbrian" Cooperative Study. Semin Oncol 6 [Suppl 7]: 52
12. Dejager R, Longeval E, Klastersky J (1980) High-dose cisplatin with fluid and mannitol-induced diuresis in advanced lung cancer: a phase II clinical trial of the EORTC Lung Cancer Working Party (Belgium). Cancer Treat Rep 64: 1341
13. Dhingra HM, Valdivieso M, Carr DT, Chiuten DF, Farha P, Murphy WK, Spitzer G, Umsawasdi T (1985) Randomized trial of three combinations of cisplatin with vindesine and/or VP-16-213 in the treatment of advanced non-small cell lung cancer. J Clin Oncol 3: 176
14. Eagan RT, Ingle JN, Creagan ET, Frytak S, Kvols LK, Rubin J, McMahon RT (1978) VP-16-213 chemotherapy for advanced squamous cell carcinoma and adenocarcinoma of the lung. Cancer Treat Rep 62: 843
15. Einhorn LH, Loehrer PJ, Williams SD, Meyers S, Gabrys T, Nattan SR, Woodburn R, Drasga R, Songer J, Fisher W, Stephens D, Hui S (1986) Random prospective study of vindesine versus vindesine plus high-dose cisplatin versus vindesine plus cisplatin plus mitomycin C in advanced non-small cell lung cancer. J Clin Oncol 4: 1037
16. Gandara D, Wold H, Perez E, Deisseroth A, Doroshow J, Meyers F, McWhirther K, Hannigan J, DeGregorio M (1988) Single agent very high-dose cisplatin (200 mg/m^2/cycle) in non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 7: 196
17. Gralla RJ, Kris MG (1988) Chemotherapy in non-small cell lung cancer: results of recent trials. Semin Oncol 15 [Suppl 4]: 2
18. Gralla RJ, Casper ES, Kelsen DP, Braun DW, Dukeman ME, Martini N, Young CW, Golbey RB (1981) Cisplatin and vindesine combination chemotherapy for advanced carcinoma of the lung: a randomized trial investigating two dosage schedules. Ann Intern Med 95: 414
19. Joss RA, Cavalli F, Goldhirsch A, Mermillod B, Brunner KW (1984) New agents in non-small cell lung cancer. Cancer Treat Rev 11: 205
20. Klastersky J (1986) Therapy with cisplatin and etoposide for non-small cell lung cancer. Semin Oncol 13 [Suppl 3]: 104
21. Klastersky J, Sculier JP, Burreau G, Libert P, Ravez P, Vandermoten G, Thiriaux J, Lecomte J, Cordier R, Dabouis G, Brohee D, Themelin L, Mommen P (1989) Cisplatin versus cisplatin plus etoposide in the treatment of advanced non small cell lung cancer. J Clin Oncol 7: 1087

22. Kramer BS, Birch R, Greco A, Prestridge K, DeSimone P, Omura G (1988) Randomized phase II evaluation of iproplatin (CHIP) and carboplatin (CBDCA) in lung cancer. A Southeastern Cancer Study Group Trial. Am J Clin Oncol 11: 643
23. Kreisman H, Ginsberg S, Propert KJ, Richards F, Graziano S, Green M (1987) Carboplatin or iproplatin in advanced non-small cell lung cancer: a Cancer and Leukemia Group B study. Cancer Treat Rep 71: 1049
24. Kyriazis AP, Yagoda A, Kyriazis AA, Fogh J (1985) Response of nude mouse-grown human urothelial cancer to *cis*-diammine-dichloroplatinum(II), diammine(1,1-cyclobutanedicarboxylato(2-)-0,0′-platinum) and mitoguazone dihydrochloride. Cancer Res 45: 2012
25. Kyriazis AP, Kyriazis AA, Yagoda A, Fogh J (1985) Response of nude mouse-grown adenocarcinomas of the human exocrine pancreas to *cis*-diamminedichloroplatinum(II), diammine(1,1-cyclobutanedicarboxylatoplatinum(2-)-0,0′-platinum and mitoguazone dihydrochloride. Cancer Res 45: 4354
26. Loehrer PJ, Birch R, Kramer BS, Greco FA, Einhorn LH (1986) Ifosfamide plus *N*-acetylcysteine in the treatment of small cell and non-small cell carcinoma of the Lung: a southeastern Oncology Study Group Trial. Cancer Treat Rep 70: 919
27. Niederle N, Schuette J, Hansmann E, Hoefeler H, Seeber S (1985) High-dose etoposide in patients (pts) with extensive disease non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 4: 181
28. Olver IN, Donehower RC, Van Echo DA, Ettinger DS, Aisner J (1986) Phase II trial of carboplatin in non-small cell lung cancer. Cancer Treat Rep 70: 421
29. Paccagnella A, Brandes A, Pappagallo GL, Simioni G, Fosser VP, Vinanate O, Salvagno L, De Besi P, Sileni VA, Fornasiero A, Fiorentino MV (1986) Cisplatin plus vindesine versus cisplatin plus VP16 versus doxorubicin plus cytoxan in non-small cell carcinoma of the lung. A randomized study. Tumori 72: 417
30. Pastran Z, Le Chevalier T, Baldeyrou P, Spielmann M, Arriagada R, Droz JP, Rouesse J (1988) Phase II study of high dose ifosfamide plus mesna in inoperable non-small cell lung carcinoma. Eur J Cancer Clin Oncol 24: 1073
31. Preusser P, Achterrath W, Niederle N, Seeber S (1985) Cisplatin. Arzneimitteltherapie 2: 50
32. Rosso R, Salvati F, Curcio CG, Belli M, Ardizzoni A, Tonachella R, Cruciani A, Colantuoni G, Bonsignore G, Saccani F, Logroscino C, Soresi E, Botta M, Scoditti S, Rubagotti A, Fusco V, Portalone L, Santi L, for the Italian Lung Cancer Task Force (FONICAP) (1988) Etoposide ± cisplatin in the treatment of advanced non-small cell lung cancer (NSCLC): a FONICAP randomized trial. Lung Cancer 4 [Suppl]: A 124
33. Sørensen JB, Østerlin K, Hansen HH (1987) Vinca alkaloid in the treatment of non-small cell lung cancer. Cancer Treat Rev 14: 29
34. Wiltshaw E, Smales E, Gallagher CJ, Staffurth J (1986) Carboplatin (Paraplatin) in ovarian cancer. Lectures and Symposia of the 14th International Cancer Congress, Budapest, vol 9, p 3