Anti-Cancer Drugs 2000, **11,** pp. 117–121

Clinical report

Monthly gemcitabine (days 1, 8 and 15) plus cisplatin (days 1–3) in advanced non-small cell lung cancer: a phase II study

Ofer Merimsky,[1] Nely Wigler,[1] Yoel Greif,[2] Yehuda Schwartz,[2] Noam Asna,[1] Joseph Paz,[3] Avraham Mann[2] and Moshe Inbar[1]

[1]Department of Oncology, Institute of Pulmonology, and [2]Department of Chest Surgery, Tel-Aviv Sourasky Medical Center affiliated with [3]Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv 64239, Israel.

On the basis of the reported efficacy of gemcitabine plus cisplatin in patients with non-small cell lung cancer (NSCLC), this combination has been selected to be given as our first-line service regimen for advanced or metastatic disease. Patients recruitment was almost unlimited: no exclusion criteria were made, except for disease-related Karnofsky's performance status below 50%, the presence of central nervous system or spinal involvement by uncontrolled metastases, or creatinine clearance below 50 ml/min. Cisplatin 30 mg/m^2/day on days 1–3 and gemcitabine 1250 mg/m^2/day on days 1, 8 and 15 every 4 weeks were given on an outpatient schedule to consecutive patients with locally advanced or metastatic NSCLC. Forty-three successive NSCLC patients with histologically or cytologically proven disease were treated. Adenocarcinoma was diagnosed in 35% of cases, squamous cell carcinoma in 60% and broncho-alveolar type in 5%. Smoking was mentioned by 63% of the patients. Numerous medical problems were recorded in 75% of the patients. Stage IIIB was observed in 10 of 43 patients, while metastatic disease was found in the rest. All the patients, except for two, were symptomatic. Two patients achieved complete response (5%) and 16 achieved partial response (37%), yielding an overall objective response rate of 42%. Minimal response was observed in seven patients (16%) and disease stabilization in 7%. Adding the objective response rate to the minimal response and stabilization rates, the disease-control (progression-free) rate reaches 65%. The time to progression ranged from 0 to 69 weeks in all the patients. The overall survival of the group ranged from 4 to 98 weeks, with a median of 45 weeks. Clinical benefit response was observed mainly in patients who also achieved an objective response. We conclude that outpatient cisplatin plus gemcitabine combination is feasible, efficacious and justified in patients with advanced or metastatic NSCLC. [© 2000 Lippincott Williams & Wilkins.]

Key words: Cisplatin, clinical benefit response, gemcitabine, non-small cell lung cancer.

Introduction

Non-small cell lung cancer (NSCLC) remains one of the most dreadful cancers in humans. The cure rate is low while the mortality rate is high. The majority of the patients are diagnosed at advanced stages, i.e. IIIB or IV, in which case the disease is not surgically curable, but amenable to chemotherapy with or without radiation therapy.[1] New hope for successful treatment of NSCLC has been generated by the emergence of new chemotherapeutic agents such as gemcitabine, vinorelbine, docetaxel and paclitaxel. Monotherapy or cisplatin-based chemotherapy with these agents were shown to be superior to best supportive care in terms of survival and quality of life.[2]

Cisplatin and gemcitabine combination has been recently accepted as a treatment option for NSCLC. The reported response rates range between 40 and 50%, and 1-year survival between 35 and 60%.[1] On the basis of the reported efficacy of gemcitabine plus cisplatin in patients with NSCLC, this combination has been selected to be given as our first-line regimen for advanced or metastatic disease. The new issue of this phase II study is its adaptation to be given as an outpatient regimen, while at the same time meeting all needs of hydration and diuresis. This article summarizes the daily experience gained with gemcitabine–cisplatin in consecutive patients with NSCLC.

Correspondence to O Merimsky, Department of Oncology, Tel-Aviv Sourasky Medical Center, 6 Weizman Street, Tel-Aviv 64239, Israel.
Tel: (+972) 3 697 4830; Fax: (+972) 3 697 4828;
E-mail: merimsky@zahav.net.il

Methods

Cisplatin 30 mg/m^2/day on days 1–3 and gemcitabine 1250 mg/m^2/day on days 1, 8 and 15 every 4 weeks were given on an outpatient schedule to consecutive patients with locally advanced or metastatic NSCLC. Vigorous hydration was based on 2000–2500 ml of 0.9% NaCl plus 1.5 g KCl/l of infused saline. Forced diuresis was maintained by 20 mg furosemide injected after each liter of fluids. Patients recruitment was almost unlimited: no exclusion criteria were made, except for disease-related Karnofsky's performance status below 50%, the presence of central nervous system or spinal involvement by uncontrolled metastases, or creatinine clearance below 50 ml/min. Baseline evaluation included medical interview, physical examination, and ancillary radiological and blood tests (plain chest film, chest and abdomen CT scan, bone scan, biochemistry panel, CEA level, and complete blood count), for documentation of patient's status and extent of the disease. Two to three courses of treatment were given until first evaluation of response and toxicity was done. If no progression was found, treatment was continued up to six cycles. Further evaluation was carried out on clinical basis or at the end of the sixth cycle. Response and toxicity were reported according to the WHO criteria. Clinical benefit response (CBR) was evaluated according to disease-related symptoms. CBR usually represents the subjective benefit from the treatment and cannot be measured by ancillary tests. CBR is assessed on the basis of improvement of performance status, weight gain, alleviation of cough, dyspnea, hemoptysis, pain and improvement of the patient's well-being.

Statistical analysis included descriptive statistics, survival analysis, and calculation of dose intensity (DI: mg of drug per squared meter body surface per week: mg/m^2/week), relative dose intensity (RDI: the ratio between given DI to the planned DI calculated separately for each drug) and average relative dose intensity (ARDI: the average of the RDI for all the drugs in the protocol, i.e. average of RDI of gemcitabine and RDI of cisplatin).

Gemcitabine and cisplatin dosage adjustments were performed according to hematopoietic and renal function before each administration. Treatment delay was preferred when hematopoietic function indicated dosage reduction of 50% or more. Patients who required a day 15 delay of more than 2 weeks due to thrombocytopenia had their next cycle on recovery of blood counts but day 15 was omitted from the rest of the courses of treatment. Patients who required a delay of more than 4 weeks for any drug were to be withdrawn from the protocol.

Patients

Forty-three successive NSCLC patients (14 females and 29 males) aged 26–78 years (median 64 years; 11 of 43 older than 70 years) were treated by gemcitabine–cisplatin combination. All had histologically or cytologically proven NSCLC. Adenocarcinoma was diagnosed in 35% of cases, squamous cell carcinoma in 60% and broncho-alveolar type in 5%. Smoking was mentioned by 63% of the patients. Numerous medical problems were recorded in 75% of the patients, including cardiovascular problems (e.g. ischemic heart disease, hypertension, peripheral vascular disease and rheumatic valvular disease), pulmonary diseases (e.g. chronic bronchitis, asthma and idiopathic pulmonary fibrosis), hepatitis B or C, peptic disease, diabetes mellitus, psoriasis, nephrolithiasis, retinal degeneration and depression. Other malignancies were reported by three patients, including breast cancer, transitional carcinoma of the bladder and papillary cancer of the thyroid—all after curative treatment and presently with no evidence of disease. Only 25% of the patients were otherwise healthy. The Karnofsky's performance status ranged from 50 to 90% (median 75%). Stage IIIB was observed in 10 of 43 patients (of whom one had undergone thoracotomy for clinical stage IIIA which turned out to be IIIB), while metastatic disease was found in 33 patients (of whom 25 patients had stage IV at presentation and eight had had cure-intended thoracotomy for the primary tumor and subsequently developed metastatic disease). All the patients were chemonaive and had not received neo-adjuvant or adjuvant chemotherapy nor treatment for relapsing disease. All the patients, except for two, were symptomatic. Weakness was reported by 77%, cough by 75%, pain by 51%, dyspnea by 44% and hemoptysis by 19%.

Results

Forty-two patients out of 43 were evaluable for toxicity and response. Results were analyzed on an intent-to-treat basis. A total of 165 courses of cisplatin (mean 3.8 per patient) and 147 of gemcitabine (mean 3.4 per patient) were administered. The given dose intensity of cisplatin was 6.75–26.8 mg/m^2/week (mean 17.9) and of gemcitabine 281–927 mg/m^2/week (mean 655). The relative dose intensity was 0.3–1.2 (mean 0.8) for cisplatin and 0.3–0.99 (mean 0.7) for gemcitabine. The average relative dose intensity for cisplatin and gemcitabine was 0.3–1.0 (mean 0.75). Two patients achieved complete response (5%) and 16 achieved partial response (37%),

yielding an overall objective response rate of 42%. Minimal response was observed in seven patients (16%) and disease stabilization in 7%. Adding the objective response rate to the minimal response and stabilization rates, the disease-control (progression-free) rate reaches 65%. The period of time to progression ranged from 0 to 69 weeks in all the patients (median 18 weeks). The overall survival of the group ranged from 4 to 98 weeks, with a median of 45 weeks. CBR was observed mainly in patients who also achieved an objective response. Responses were more frequent in males (15 of 29 versus three of 14; statistically insignificant), in patients with squamous cell type cancer versus other types (13 of 26 versus five of 17; statistically insignificant) and in those who had not undergone thoracotomy for the primary tumor (17 of 34 versus none of nine; $p < 0.05$). Considering the eight patients who had undergone cure-intended thoracotomy and received gemcitabine plus cisplatin for recurrent or metastatic disease, the response rate was only 12.5% (one partial response for 25 weeks and one stable disease for 19 weeks). CBR was observed only in the patient who had a partial response.

No correlation could be found between the RDI and the ARDI of each individual to the type or response nor to the duration of response or time to progression.

CBR (to any extent) was reported by 50% of the patients. Cough was alleviated (completely or partially) in 50%, pain in 46%, dyspnea in 45%, hemoptysis in 39% and well being was improved in 53%. Toxicity was acceptable, except for one case of cardiogenic shock and death soon after the end of the first gemcitabine infusion, and one patient with neutropenic fever and pneumonia who died after massive aspiration of gastric content. Deep vein thrombosis was observed in three patients and acute hepatitis in one hepatitis B carrier patient was also noted. Grade 3–4 hematological toxicity was common: neutropenia was observed in 21%, including one case of neutropenic fever (mentioned above), thrombocytopenia in 56% and drop in hemoglobin in 19%. Other grade 3–4 toxic symptoms were nausea in 16%, fatigue in 28%, alopecia (grade 2 for total alopecia) in 90% and peripheral neuropathy in 9% of the patients.

Discussion

Gemcitabine and cisplatin combination chemotherapy has been applied on an outpatient schedule to a non-selected population of consecutive patients with advanced or metastatic NSCLC and rich medical history. The response rate, median survival and relatively low toxic profile achieved by the gemcitabine–cisplatin regimen in this study and the median survival merits its use as a service protocol for NSCLC, even though its superiority over other new combinations has not been proven yet.

The response rate observed in this phase II study was 42% and the median survival was 10 months. However, patients with dreaded diseases like NSCLC are not always interested in pure response rates or other dry figures, as clinicians and statisticians, but rather in the possibility to arrest or control the disease and to alleviate symptoms. This is why CBR was mentioned by several authors and why in this study we also referred to a disease-control or progression-free rate of 65%. The statistical analysis in our study was, however, based on the traditional definitions of response.

Chemotherapy has been advocated in NSCLC since it has been found to be superior to best supportive care in terms of survival and cost. The absolute benefit on survival was not striking, i.e. an addition of 1.5 months and a 10% increase in 1-year survival.[3] Cisplatin, mitomycin C and ifosfamide, as well as cisplatin plus etoposide, were shown to be better than supportive care.[4,5] After showing that gemcitabine monotherapy yielded promising results,[6–8] gemcitabine was combined with cisplatin.[9–14] The response rate attributed to gemcitabine plus cisplatin ranges from 30 to 54%, with a median survival time of 6–10.7 months.[9–14]

The combination of cisplatin and gemcitabine was found to be superior to other commonly used chemotherapy combinations such as mitomycin, ifosfamide and cisplatin (MIC).[15] Whereas the overall response rate was 40% in the GP arm with two complete responses it was only 28% in the MIC arm with one complete response (p=0.03). MIC was found to be more toxic than GP. Median survival time was 35 weeks in GP and 38 weeks in the MIC arm.[15]

Gemcitabine plus cisplatin was also found to be superior also to etoposide plus cisplatin. The response rate of gemcitabine plus cisplatin was significantly higher than in the old combination (40.6 versus 21.9%; p=0.02), the time to progression was longer for gemcitabine plus cisplatin (6.9 versus 4.3 months; p=0.01) but the impact on survival was disappointing (8.7 versus 7.2 months; p=0.18).[16]

The optimal schedule for the gemcitabine–cisplatin combination is still undetermined. In our study cisplatin was given on days 1–3 while gemcitabine was given on a more conservative schedule. The response rate and median survival did not differ from other series with different schedules. The total dose of platinum was divided over 3 days in order to

administer the agent at a relatively high total dose in the day-care, and to avoid severe emesis and the risk for congestive heart failure during intensive rehydration (2000–2500 ml 0.9% NaCl on 1 day). Data from six studies of combination gemcitabine plus cisplatin therapy in NSCLC were analyzed by Shepherd *et al.*[17] to assess the impact of various prognostic factors including cisplatin schedule, performance status, gender, disease stage and histology upon response rate and survival. In all the studies gemcitabine 1000–1500 mg/m^2 was administered over 30 min on days 1, 8 and 15 every 4 weeks. Cisplatin 100 mg/m^2 was given on day 1 or 2 or 15, or 30 mg/m^2 on days 1, 8 and 15. The response rates ranged from 28 to 54% and the survival ranged from 8.4 to 15.4 months. Standard prognostic factors all trended in the expected direction, and the only *statistically significant* variables were cisplatin schedule and gender. Logistic regression analysis showed that cisplatin delivery on day 2 or 15 was associated with a better response rate (42 versus 29%; p=0.034) than delivery on day 1 or days 1, 8 and 15. Cox regression analysis showed that survival was better for cisplatin on day 2 or 15 (hazard ratio 0.647, p=0.002) and female gender (hazard ratio 0.665, p=0.013).[17]

In our study, the dose intensity of cisplatin and gemcitabine did not correlate with the results in terms of response type and duration. Several patients with impressive response achieved moderate dose intensity, while some of those who were treated with a full dose intensity showed only a modest response. Moreover, the mean average relative dose intensity for cisplatin and gemcitabine was only 0.75, which resulted from dose reduction or treatment delay because of bone marrow toxicity, while our observed response rate was in the range of 40%. This observation raised a question concerning the role of dose intensity of gemcitabine and cisplatin in NSCLC. It is possible that even lower doses and lower dose intensity may yield the same results in patients with NSCLC.

The next step of this study is administration of cisplatin 30 mg/m^2/day on days 1 and 2, and gemcitabine 1250 mg/m^2/day on days 1 and 8 every 3 weeks. This schedule yields approximately the same dose intensity as our basic regimen given every 4 weeks. The meaning of the dose reduction is an attempt to minimize the toxicity in order to preserve quality of life and at the same time to maintain the expected results at a range of 40%. Results are now awaiting maturation.

In conclusion, outpatient cisplatin plus gemcitabine combination is feasible, efficacious, relatively non-toxic and justified in patients with advanced or metastatic NSCLC even in the presence of other medical problems. The combination should be further tested versus other modern combinations and in the pre-operative (induction) or adjuvant set-up.

References

1. Bunn PA, LeChevalier T. Lung cancer research: new combinations and the emerging role of gemcitabine. *Semin Oncol* 1998; **25** (suppl 9): 1.
2. NSCLC Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. *Br Med J* 1995; **311**: 899–909.
3. Rapp E, Pater JL, Willan A. Chemotherapy can prolong survival in patients with advanced non-small cell lung cancer. Report of a Canadian multicenter randomized trial. *J Clin Oncol* 1988; **6**: 633–41.
4. Cullen MH, Joshi R, Chetiyawardana AD, Woodroffe CM. Mitomycin, ifosfamide and *cis*-platin in non-small cell lung cancer: treatment good enough to compare. *Br J Cancer* 1988; **58**: 359–61.
5. Einhorn LH, Loehrer PJ, Williams SD, *et al*. 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* 1986; **4**: 1037–43.
6. Abratt RP, Bezwoda WR, Falkson G, *et al*. Efficacy and safety profile of gemcitabine in non-small-cell lung cancer: a phase II study. *J Clin Oncol* 1994; **12**: 1535–40.
7. Anderson H, Lund B, Bach F, Thatcher N, Walling J, Hansen HH. Single-agent activity of weekly gemcitabine in advanced non-small-cell lung cancer: a phase II study. *J Clin Oncol* 1994; **12**: 1821–6.
8. Gatzemeier U, Shepherd FA, Le Chevalier T, *et al*. Activity of gemcitabine in patients with non-small cell lung cancer: a multicentre, extended phase II study. *Eur J Cancer* 1996; **32A**: 243–8.
9. Abratt RP, Bezwoda WR, Goedhals L, Hacking DJ. Weekly gemcitabine with monthly cisplatin: effective chemotherapy for advanced non-small-cell lung cancer. *J Clin Oncol* 1997; **15**: 744–9.
10. Anton A, Carrato A, Gonzalez-Larriba JL. Phase II activity of gemcitabine in combination with cisplatin in advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* 1996; **15**: 380 (abstr 1134).
11. Crino L, Scagliotti G, Marangolo M, *et al*. Cisplatin–gemcitabine combination in advanced non-small-cell lung cancer: a phase II study. *J Clin Oncol* 1997; **15**: 297–303.
12. Sandler A, Crino L, Steward WP. Extended survival in stage III and IV non-small cell lung cancer (NSCLC) patients treated with gemcitabine plus monthly cisplatin. *Ann Oncol* 1996; **7**: 91a.
13. Shepherd FA, Burkes R, Cormier Y, *et al*. Phase I dose-escalation trial of gemcitabine and cisplatin for advanced non-small-cell lung cancer: usefulness of mathematic modeling to determine maximum-tolerable dose. *J Clin Oncol* 1996; **14**: 1656–62.
14. Steward WP, Dunlop DJ, Dabouis G, Lacroix H, Talbot D. Phase I/II study of gemcitabine and cisplatin in the treatment of advanced non-small cell lung cancer: preliminary results. *Semin Oncol* 1996; **23** (5 suppl 10): 43–7.

15. Crino L, Conte P, De Marinis F. A randomized trial of gemcitabine cisplatin versus mitomycin, ifosfamide, and cisplatin (MIC) in advanced non-small cell lung cancer (NSCLC): a multicenter phase III study. *Proc Am Soc Clin Oncol* 1998; **17**: 455 (abstr 1750).
16. Cardenal F, Paz Lopez-Caberizo M, Anton A, *et al*. Randomized phase III study of gemcitabine–cisplatin in the treatment of locally advanced or metastatic non-small cell lung cancer. *J Clin Oncol* 1999; **17**: 12–8.
17. Shepherd FA, Anglin G, Abratt R, *et al*. Influence of gemcitabine (Gem) and cisplatin (CP) schedule on response and survival in advanced non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 1998; **17**: 472a (abstr 1816).

(Received 5 October 1999; revised form accepted 7 December 1999)