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CLINICAL TRIALS REPORT

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Symptomatic, stage IV, non-small-cell lung cancer (NSCLC): response, toxicity, performance status change and symptom relief in patients treated with cisplatin, vinblastine and mitomycin-C

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Abstract In a series of 46 symptomatic patients with metastatic, stage IV, non-small-cell lung cancer (NSCLC), we used a three-drug combination with cisplatin (120 mg/m^2), vinblastine (6 mg/m^2) and mitomycin-C (6 mg/m^2) (PVM), repeated every 3 weeks. After two courses, we observed that none of the patients had achieved a complete response; 33% (15/46) had partial response (95% confidence limits: 19.2–46.8); 39% (18/46), stable disease and 28% (13/46), progressive disease. Median response duration was 14.0 weeks (range, 4–36.7), median time to progression 22.4 weeks (range, 7–44.4), and median survival time 26.4 weeks (range, 1–103). WHO grade III–IV myelotoxicity occurred in 15.2% of the courses administered, affecting 39.5% of patients, and severe nephrotoxicity was observed in 9.3% of patients. No toxic death occurred. The post-treatment KPS score increased in 7 patients with partial response (47%), 4 with stable disease (22%) and 1 with progressive disease (8%), while it decreased in 3 patients with partial response (20%), 3 with stable disease (17%) and 10 with progressive disease (77%). In all, KPS increased in 12/46 cases (26%). However, no statistically significant difference was observed when the KPS score before and after treatment was compared in the total group of patients or when it was compared in responders and in non-responders. After chemotherapy, there was complete disappearance of at least one symptom in 27.1% of cases and improvement in 27.1%. Overall, major symptom control occurred in 54.3% of cases, with a median palliation time lasting 10 weeks (range, 4–32). Patients with partial remission and stable disease achieved symptomatic palliation in 90% and 55.5% of cases, respectively. When we compared the palliation rate between responders and non-responders, a significant difference was noted (Chi-square test: $P < 0.05$). Although our schedule did not produce a higher objective response rate and the KPS score was not significantly improved, the symptom palliation appeared worthwhile considering the highly unfavourable prognosis of the patients investigated.

Key words Lung neoplasms · Non-small-cell lung cancer Chemotherapy · Palliative treatment · Performance status

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Introduction

Chemotherapeutic treatment of metastatic non-small-cell lung cancer (NSCLC) still remains a major challenge. Cisplatin-based combinations including mitomycin-C and vinca alkaloids (PVM) or ifosfamide (MIC) have shown a high response rate. Nevertheless, drug toxicity remains substantial and survival improvement uncertain. So far, no standard regimen exists, and indeed, the decision to treat a patient for metastatic disease remains controversial. However, there are good reasons for chemotherapy. Response to therapy occurs early, and treatment that proves ineffective or toxic can be suspended quickly; the disease does not have an indolent course since the tumour growth causes toxicity; patients responsive to therapy often achieve symptom relief and longer survival.

Although studies on chemotherapy are numerous, endpoints other than response rates and survival have not been extensively explored in NSCLC [15]. Some studies in the literature suggest that combination chemotherapy can control cancer symptoms and improve performance status in patients [16, 17]. However, the data available are not extensive, and further investigations are necessary.

In the present study, we evaluated the activity of a high-dose cisplatin schedule in a group of symptomatic patients with metastatic NSCLC. In particular, we attempted to assess to what extent chemotherapeutic treatment of these

poor-risk patients may influence both performance status and symptom palliation.

Patients and methods

Between January 1989 and December 1992, 46 patients (35 male and 11 female) with cytologically or histologically proven NSCLC were enrolled. The main inclusion criteria were: metastatic, stage IV, disease; no previous chemotherapy or radiotherapy; evaluable disease; Karnofsky performance status (KPS) score 60–100; normal blood counts and chemistries; normal cardiac, liver and renal functions. Before entering the study, patients gave verbal informed consent. Patients with central nervous system (CNS) metastases were also included in the study. At the time of diagnosis, all patients suffered from at least one tumour-associated symptom. Prior to therapy, all patients underwent standard staging procedures, and they were staged according to the Mountain's classification [20]. Patient assessment included: case history, physical examination, sign and symptom evaluation and tumour measurements. Instrumental examinations were: chest X-rays and CT scan, bronchoscopy, bone scintiscan and abdominal echography; other imaging techniques were used as required. Restaging procedures were repeated every 3 weeks. PVM schedule consisted of: cisplatin, 120 mg/m^2, i. v. on day 1, with 4 h hydration and furosemide-induced diuresis; vinblastine, 6 mg/m^2 i. v. on day 1 and mitomycin-C, 6 mg/m^2 i. v. on day 1. Courses were repeated every 3 weeks until progression. A minimum of two courses were delivered before evaluation of response, except in cases with clear disease progression. A reduction of drug doses or a delay in drug administration was planned according to myelotoxicity or other side-effects; toxicity was graded according to WHO criteria [19]. To prevent nausea and vomiting, patients received ondansetron before and for 2 days after chemotherapy. CNS metastases were treated with anti-edemagen agents and subsequently with cranial irradiation when required. Tumour response to therapy was classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) according to the international WHO criteria. Response duration was evaluated from the first evidence of tumour regression up to disease progression, and time to progression from the start of chemotherapy up to progression. Median survival of patients was evaluated by life-tables starting from the beginning of treatment.

Palliative treatment

On admission all patients complained of one or more tumour-related symptom they had been suffering from for at least 6–8 weeks. As palliation, patients were receiving various symptomatic agents, summarised as follows: diclofenac, 100–200 mg daily (10 patients); dihydrocodeine, 30–60 mg daily (10 patients); indomethacin, 50–75 mg daily (8 patients); acetaminophen, 500–1000 mg daily (7 patients); theophilline, 300–600 mg daily (6 patients). Furthermore, 37 out of the 46 patients were receiving additional doses of corticosteroids: dexamethasone, 4–8 mg daily (8 patients); and deflazacort, 6–30 mg daily (29 patients). No modification in doses and schedules of symptomatic care were introduced during the treatment with PVM combination.

Following PVM chemotherapy, palliative radiotherapy was given if clinically required. Unresponsive patients who needed local tumour control and those who did not improve after chemotherapy were candidates for symptomatic radiotherapy.

Assessment of palliation

Symptom grading (listed in Table 2) and KPS score were assessed on admission and after each course of PVM. Further evaluations of both symptoms and KPS change were recorded at each patient attendance. No extensive questionnaires were required. The following categories were used as simple criteria to assess symptom palliation: (1) disappeared: complete disappearance of symptoms; (2) improved: good symptomatic improvement; (3) unchanged: no symptomatic improvement; (4) worse: progression of symptoms. The patients were asked to report the changes in their symptoms choosing the category in which they belonged.

Physicians collected results according to the patients' indications. After chemotherapy, the assessment of symptoms and the degree and direction of change were expressed as number of symptoms, at least one, fitting in any of the above categories; the differences in KPS, in the entire group of patients and between subgroups, were statistically compared by means of the Mann-Whitney U-test and the Wilkoxon rank sum test. Symptom palliation rates by response categories were compared by means of Chi-square statistics. Duration of palliation was calculated as the mean time for which patients suffered no symptoms.

Table 1 Characteristics of patients

No. of patients	46
M/F	35/11
Median age (range)	60 (42–70)
Karnofsky	
100	6
90–80	27
70–60	13
Histology	
Epidermoid	15
Adenocarcinoma	23
Undifferentiated	8
Metastases	
One	10
Two or more	36
Involved sites	
Bone	22
Lymph nodes	11
Liver	10
Lung	10
Adrenal	9
Pleural effusion	8
Brain	8

Results

Forty-six patients entered the study. Two died soon after the first cycle of chemotherapy and were considered early deaths (ED). Three further patients were considered failures, since they refused therapy after the first course because of severe toxicity. However, all patients were evaluated for response and survival.

The characteristics of patients are reported in Table 1. Most patients (72%) had favourable KPS (80–100), adenocarcinoma histotype (50%), and multisite involvement (78%). Bone was the most highly involved site (48%), followed by lymph nodes (24%). Both pleural effusion and brain involvement were rather frequent (17%). Symptoms and their frequency in all patients, and the palliation achieved with treatment are summarized in Table 2. Pain was the most frequent symptom reported (39%). It was described as spinal pain (17%) or chest wall pain (22%); other significant symptoms were asthenia (35%) and weight loss by over 5% in the last 3 months (28%). Of the 8 patients

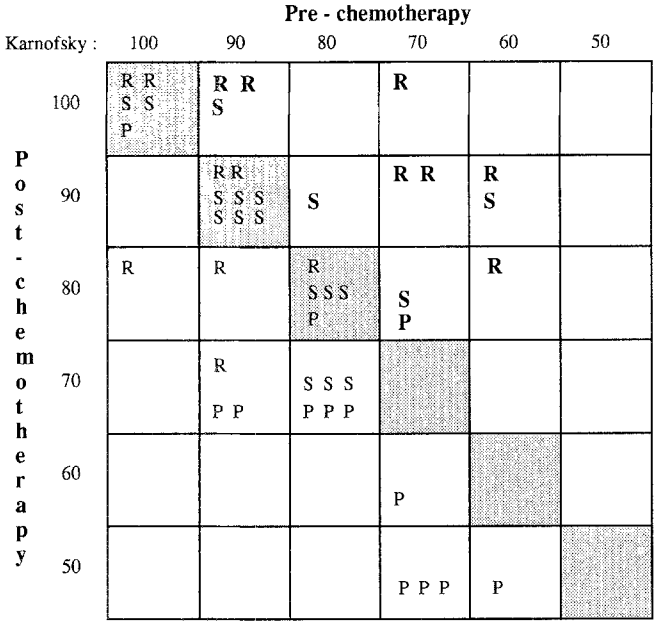

Fig. 1 Changes of Karnofsky Performance Status in the 46 patients. Figures in bold print are the improved cases: *R*, responders; *S*, stable disease; *P*, progressive disease. Pre- and post-treatment differences among groups were not significant

with CNS metastases who complained of headache, 6 achieved a complete relief after receiving diuretics and corticosteroids. They were then excluded from the analysis of palliation. After chemotherapy, 15 patients underwent palliative irradiation (6 to the brain, 6 to the primary and 3 to bone sites).

Response and toxicity

Response was calculated according to the "intention to treat". In the 2 patients who succumbed to ED and the 3 patients who refused further chemotherapy treatment was considered to have been unsuccessful, and these patients were classed in the PD category. After chemotherapy, no case of CR was observed; PR was achieved in 33% (15/46) of patients (confidence limits: 19.2–46.8); SD was recorded in 39% (18/46); and PD, in 28% (13/46). The median duration of response (MDR) was 14 weeks (range, 4–36.7) and median time to progression (TTP) 22.4 weeks (range, 7–44.4). The median overall survival time in patients was 26.4 weeks (range 1–103). The actual cisplatin dose intensity was 100% in 43 patients and 50–75% in 3 patients. Toxicity was evaluated as number of WHO grade III–IV episodes recorded in the 43 evaluable patients (data from 3 patients were not available) after at least 1 course of PVM. Altogether, patients received 138 courses of PVM (mean 3 courses per patient, range 1–6). The incidence of severe or life-threatening leucopenia was 17% (24/138) and that of thrombocytopenia, 13% (18/138). The myelosuppression rate was 39.5% (referred to number of patients). Eight patients required blood transfusions due to symptomatic anaemia. All patients showed a mean fall of 2 g% in the haemoglobin level. Four patients showed irreversible nephrotoxicity (serum creatinine 2.5–4 mg/dl); as a result, 3 of them declined further treatment after the first course of PVM. Severe vomiting occurred in 13% (18/138) of courses; the percentage of patients showing emesis was 30.2%. Mild neurotoxicity (ototoxicity and peripheral neuropathy) was reported in 3 patients only, but this assessment was underestimated because no neurological evaluation had been performed in several instances.

Performance status and symptoms

Figure 1 illustrates the change observed in KPS between 3 and 6 weeks after completion of at least two cycles. Among the 46 patients, 12 (26%) showed an improved KPS, 18 (39%) maintained a stable KPS and in 16 (35%) the KPS worsened. KPS changes by response category were improved: 7 PR, 4 SD, 1 PD; unchanged: 5 PR, 11 SD, 2 PD (it should be noted that 2 patients with PR, 2 with SD, and 1 with PD maintained the initial KPS scored at 100); worse: 3 PR, 3 SD, 10 PD. Altogether, KPS improved in 47% of responders (7/15), in 22% of patients with stable disease (4/18), and 8% of patients in whom treatment was unsuccessful failures (1/13). On the other hand, it decreased in 20% of responders (3/15), in 17% of patients with stable disease (3/18) and in 77% of treatment failures (10/13).

In the 12 patients with improved KPS score, the pre-treatment median KPS score of 70 (range, 60–90) gave way to one of (range, 80–100) after treatment. Statistical comparison of the KPS scores of all patients before and after therapy showed no significant difference (Mann-Whitney, $P = 0.49$; Wilcoxon, $P = 0.28$). Similarly, no significant difference in KPS was detected when responders were compared with non-responders (Mann-Whitney, $P = 0.47$; Wilcoxon, $P = 0.18$).

Table 2 summarizes major symptoms and palliation obtained following chemotherapy, total of 81 symptoms were recorded, and there was a complete disappearance, of at least 1 symptom in 22 (27.1%) cases (18 PR, 4 SD) and a good improvement in 22 (27.1%) further, (9 PR, 11 SD, 2 PD) cases. Overall, there was major symptom relief in 44/81 cases (54.3%). Median duration of palliation was about 10 weeks (range, 4–32). No change in symptoms occurred in 21 (25.9%) cases (3 PR, 9 SD, 9 PD), while symptoms worsened in the remaining 16 (19.7%; 3 SD, 13 PD).

According to response categories, major palliation of at least 1 symptom (disappearance or improvement) occurred in 27/29 cases with PR (90%), in 15/27 (55.5%) with SD and in 2/24 (8%) with PD. The difference between responders and non-responders (SD and PD) in palliation rate was significant (Chi-square: $P < 0.05$). Fever and haemoptysis were the most responsive symptoms, disappearing or improving in all cases (100%). Improvement was recorded in other symptoms as follows: dyspnoea in 4/6 (67%) cases, asthenia in 10/16 (62.5%), pleural effusion in 4/8 (50%), pain in 8/18 (44%), cough in 4/10 (40%) and weight loss in 4/13 (31%).

Table 2 Symptoms in the 46 patients and palliation following chemotherapy (*P* progressive disease: *R* responders; *S* stable disease)

Symptoms	Cases	Outcome									
		Disappeared		Improved			Unchanged			Worse	
Pain	18	2R	2S	1R	2S	1P	2R	3S	3P		2P
Asthenia	16		1S	6R	3S			3S		1S	2P
Weight loss	13	2R		1R	1S		1R	1S	2P	2S	3P
Cough	10	3R			1S			1S	2P		3P
Pleural effusions	8	2R			2S			1S	2P		1P
Fever	7	5R			1S	1P					2P
Dyspnoea	6	2R		1R	1S						
Haemoptysis	3	2R	1S								
Total	81	18R	4S	9R	11S	2P	3R	9S	9P	3S	13P

Discussion

Though all our patients had a highly unfavourable prognosis, our schedule showed an interesting objective tumour response rate of 33%. However, similar results have already been observed by others. Ruckdeschel et al. [23] reported a response rate of 31%, and Bunn [3] found a mean response rate of 32% on pooling data from five large controlled trials. In this review, response to PVM varied from 20% to 54% according to the extent of disease and cisplatin dose intensity. In recent experience, when cisplatin doses were increased to 75–100 mg/m^2, the response rate increased although no better dose-response curve was observed with the higher doses and toxicity actually worsened [10]. Myelosuppression with our schedule was substantial (39.5%) but was well controlled and led to no secondary deaths. In other studies using similar or less intensive cisplatin-based combinations, the incidence of severe myelotoxicity was 20–30%, and that of nephrotoxicity 10–20%; drug-related deaths occurred in from 4% to 10% of the patients [5, 22].

The effect of chemotherapy on KPS varied according to response categories. KPS improved in about half of the responders and in a quarter of the patients, with stable disease, while it worsened in the group with progressive disease. On the other hand, a subset of both responders (20%) and stable disease patients (17%) showed worsening of KPS despite improvement of the disease. It is probable that toxicity from chemotherapy affected KPS in these cases. Accordingly, a lower cisplatin dose than the one we used may be advisable. However, in the present study, cumulative KPS benefit before and after the treatment appeared modest (26%); comparison of neither patients as a whole nor responders vs non-responders revealed any significant difference. Cullen et al. [6] reported an identical 27% of cases with improved KPS when considering all treated patients, but responders achieved a significantly higher KPS than non-responders. More favourable data were observed by Kris et al. [17] who, after treatment, observed an increased KPS in 44% of cases, and by Martoni et al. [18], who found KPS improvement in up to 65% of their patients. In contrast, Bakker et al. [1], in a small study on 27 patients, found a significant reduction in KPS and body weight both in responders and in non-responders during chemotherapy. According to these authors, the deterioration of patients' wellbeing offset any potential advantage from treatment.

The role of radiotherapy in symptom palliation is well known and accepted in the literature; it has an especially high palliative capacity (70–80%) in treating symptoms relating to local disease [21]. Our data suggest that chemotherapy could also have a role in symptom palliation in patients with widespread disease. In fact, in our series, symptoms improved or disappeared in more than half of all cases. This was clearer in responsive disease (90%), and less so but still significant in cases of stable disease (55.5%). Kris et al. [17], measuring cough, dyspnoea, pain and haemoptysis, found that all these symptoms improved significantly with chemotherapy. Hardly et al. [16], treating 24 patients with PVM, recorded a response rate of 21%, but noted that 75% of patients had symptomatic control, including 21% who achieved complete relief. In this experience the benefit lasted 7 weeks, as against 10 weeks in our study.

In conclusion, with our treatment KPS did not increase significantly, but symptom palliation appeared highly worthwhile. This fact may be of relevance in the decision to treat a patient with unresectable advanced disease.

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