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Mitomycin C, vinblastine and cisplatin combination chemotherapy in the treatment of advanced non-small cell lung cancer

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Summary. Thirty-one patients with previously untreated advanced non-small cell lung cancer were treated with mitomycin C (10 mg/m^2, day 1), vinblastine (5 mg/m^2, days 1 and 15), and cisplatin (80 mg/m^2, day 1). Combination chemotherapy was repeated at 4-week intervals until disease progression or unacceptable toxicity. The overall response rate was 52.0%, with a median survival time of 8 months. The median duration of response was 16 weeks (range, 7–49 weeks), and 23% of the patients survived for more than 1 year. Toxicity included moderate myelosuppression, mild nephropathy, and severe nausea and vomiting. This combination therapy of anticancer agents appears to have antitumor activity, but not to have satisfactory therapeutic activity for advanced non-small cell lung cancer.

Introduction

Despite recent advances in chemotherapy, the treatment of inoperable non-small cell lung cancer (NSCLC) remains unsatisfactory. In single-agent trials, response rates of 6%–31% for vindesine and 6%–32% for cisplatin have been reported [2]. The synergistic response rate of both drugs given concurrently has been observed [10]. Studies evaluating vinblastine with cisplatin suggested equivalent activities [4, 7, 13, 22, 24]. There have been reports of the effectiveness of mitomycin C as a single agent [17, 20] and of mitomycin C-related drug combinations [1, 3, 5, 9, 11, 14–16, 18, 19, 21]. We initiated a clinical trial with a combination of mitomycin C, vinblastine, and cisplatin in August 1983.

Patients and methods

From August 1983 to December 1985, 31 patients with histologically confirmed non-small cell lung cancer entered this study. Patient characteristics are summarized in Table 1. Criteria for entry in this study included no prior chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status of 0–3, normal marrow reserve, and acceptable renal and hepatic functions. All patients were required to have measurable or evaluable disease. Patients who had major regional morbidity, such as severe brain metastasis and superior vena caval syndrome, were excluded, since they were immediately irradiated.

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The treatment schedule was as follows; mitomycin C, 10 mg/m^2 on day 1; vinblastine, 5 mg/m^2 on days 1 and 15; and cisplatin, 80 mg/m^2 on day 1. Patients received pre- and posthydration with mannitol [12]. Cycles repeated every 4 weeks. Patients were evaluated for response after two cycles. Responding and stable patients continued therapy unless disease progression or unacceptable toxicity occurred. For patients with evaluable disease response was graded according to the data of Eagon et al. [6] as follows: complete response was the disappearance of all evidence of tumor for at least 4 weeks; partial response was greater than 50% reduction of the sum of the products of the two greatest perpendicular diameters of all measurable lesions for at least 4 weeks; stable disease was defined as less than 25% change in any measurable tumor; and criteria for progression were the appearance of new tumor lesions or the increase in measurable disease by more than 25%. Survival and duration of response were recorded from the first day

Table 1. Patient characteristics and responses

Characteristic	No. of patients	No. of responders
Entered/evaluable	31/30	
Median age in years (range)	67 (37–79)	
Sex		
Male	20	12
Female	10	4
Performance status (ECOG)		
0–1	23	14
2–3	7	2
TNM stage (UICC)		
III	13	6
IV	17	10
Histology		
Squamous cell carcinoma	9	6
Adenocarcinoma	17	10
Large cell carcinoma	4	0
Metastatic sites		
Brain	3	0
Lymph nodes	5	4
Lung	5	3
Liver	1	1
Bone	6	3
Skin	1	0

of treatment. The survival curve was calculated by the method of Kaplan and Meier.

Results

Of the 31 patients in this study, 30 received adequate chemotherapy for evaluation of therapeutic response. Patients underwent a median of three treatment cycles, with a range of one to six cycles. The median follow-up was 305 days (range, 41–745 days). Patient characteristics and responses are presented in Table 1. Measurable response occurred in 16 patients, but no patients achieved complete response. The overall response rate was 52.0%. Partial response was achieved by 67% of the patients with squamous cell carcinoma and 59% with adenocarcinoma, but 4 patients with large cell carcinoma did not respond to chemotherapy at all. The median duration of response for all responders was 16 weeks (range, 7–49 weeks). The median survival time for all patients was 8 months, though 7 of the 30 patients (23%) survived for more than 1 year.

Table 2 outlines the toxicity found during the study. Toxic effects included nausea and vomiting in all studies. Because of gastrointestinal toxicity, 1 patient refused further chemotherapy after the first course. Hematologic toxicity was generally mild. The median leukocyte count nadir for all patients was 2400/μl (range, 250–8500). Only 3 patients (9.7%) had leukocyte counts lower than 1000/μl. Dose attenuation because of thrombocytopenia was not necessary. Only 2 patients required platelet transfusions. No patient developed clinical bleeding related to thrombocytopenia. The median platelet count nadir for all patients was 132000/μl (range, 15000–260000). Thrombocytopenia of less than 50000/μl occurred in only 2 patients. The median hemoglobin nadir was 9.0 g/dl (range, 6.3–13.7). Nephrotoxicity, defined as a peak serum creatinine value above 1.5 mg/dl, occurred in 23% of patients. Only 1 patient had a rise in serum creatinine above 2.0 mg/dl (2.1 mg/dl). In all patients the serum creatinine returned to the normal range without specific treatment. Although nephrotoxicity was generally of a mild degree, as outlined in Table 2, 1 patient who received three courses of cisplatin died during an episode of oliguric renal failure. No patient had neurotoxicity or required reduction of vinblastine dose.

Table 2. Observed toxic effects in 31 patients

	No. of patients
Leukocyte (cells/mm^3)	
>4000	4
2100–4000	14
1000–2000	10
<1000	3
Platelet (cells/mm^3)	
>100000	24
50000–100000	5
<50000	2
Highest serum creatinine (mg/dl)	
>2.0	1
1.5–2.0	6
<1.5	24

Discussion

Recent trials of mitomycin C, vinca alkaloid, and cisplatin in NSCLC have shown a 26%–78% response rate [1, 9, 11, 14, 16, 18, 19, 21], but the complete response rate has remained minimal. The two vinca alkaloids, vinblastine and vindesine, appear to be equivalent in terms of response rate (27% and 23%, respectively) [13]. We found that the combination of mitomycin C, vinblastine, and cisplatin produced a response rate of 52.0% with a median survival time of 8 months in evaluable patients. The initial response to this combination chemotherapy was high enough for the therapy to be considered beneficial in the treatment of NSCLC. Although the median survival time was short, 7 of the 30 patients (23%) survived for more than 1 year. It has previously been reported that mitomycin-vinblastine-platinum had an unsatisfactory 1-year survival rate (12%) in metastatic NSCLC [8]. The discrepancy in the percentage of 1-year survivors might be due to the dose of cisplatin administered and the variety of patients. The toxicity of this regimen was mild. These data suggest that the maximum drug dose has not been reached and that further manipulation of drug dose and schedule may be possible in an attempt to enhance the effectiveness of this regimen. Nausea, vomiting, and anorexia for several weeks after a drug cycle has been a continuing problem with this drug combination. A high dose of metoclopramide moderated the early nausea and vomiting but appeared to have little effect on the long periods of anorexia seen after treatment in some patients [23]. Further studies are needed to identify new agents, to establish new combinations of individually active agents, and to define the role of radiotherapy and surgery in patients treated with chemotherapy.

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