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Clinical report

Prolonged administration of infusional cisplatin and oral etoposide in advanced non-small cell lung cancer

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We conducted a phase I/II trial to determine the maximum tolerated dose (MTD) and the efficacy of prolonged infusion of cisplatin and oral etoposide in the treatment of advanced non-small cell lung cancer (NSCLC). Cisplatin was given via an infuser in escalating doses of 5, 6.5, 8, 9 and 10 mg/m^2/day for 14 days along with etoposide at a fixed dose of 50 mg/m^2/day orally followed by a 2-week rest period. All patients had stage IIIB or IV NSCLC. A cisplatin dose of 8 mg/m^2/day was determined as the MTD. In the 13 patients treated at this dose level, grade III and IV toxicities were mainly hematologic including neutropenia (n=5), febrile neutropenia (n=4), thrombocytopenia (n=3) and anemia (n=6). Grade III/IV renal toxicity occurred in one patient. There were no treatment-related deaths. One patient had a partial response and three patients had stable disease. Thus, although the described regimen of cisplatin/etoposide is reasonably well tolerated, it does not appear to be better than the same combination administered over a shorter duration, in spite of a cumulative dose of 112 mg/ m^2 of cisplatin and 700 mg/ m^2 of etoposide per cycle. [© 2002 Lippincott Williams & Wilkins.]

Key words: Cisplatin, etoposide, lung cancer.

Introduction

Lung cancer is the most common cause of cancer death in the western world with more than half a million new cases diagnosed annually.[1,2] The 5-year survival across all stages of non-small cell lung cancer (NSCLC) is less than 15%.[2,3] The treatment of advanced NSCLC is chemotherapy based.[4] Various chemotherapeutic agents have been used in the treatment of NSCLC.[5] During the 1980s, platinum-based regimens became the standard of care. A cisplatin and etoposide combination was the regimen of choice in numerous clinical trials.[6–8] Treatment with cisplatin and etoposide is typically administered over a 3- to 4-day period every 3–4 weeks. The prolonged administration of oral etoposide was studied as a single therapy[9–10] or in combination with cisplatin given over a shorter period of time.[11–12] However, prolonged administration of both agents has not been reported. The purpose of this study was to determine whether prolonged exposure to two active and synergistic agents would improve efficacy. Prior studies suggested synergy and enhanced efficacy by prolonged administration.[15–17] One *in vitro* study revealed that lower, frequent doses of these agents was more efficacious than fewer larger doses.[18] Alternating these drugs was more effective since cisplatin resulted in recruitment of more quiescent cells into active proliferation enhancing the efficacy of subsequent etoposide treatment.[18] In this study, we report the results of a phase I/II clinical trial evaluating the tolerability and efficacy of prolonged administration of this combination in advanced NSCLC patients.

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Patients and methods

Patients

Patients with microscopically confirmed diagnosis of NSCLC and clinical stages IIIB and IV were included in this study. Southwest Oncology Group performance status of 0–2 was required, in addition to adequate pulmonary, hepatic, renal and bone marrow function. Patients with central nervous system involvement or patients who received prior chemotherapy or radiotherapy treatment were excluded.

The study was conducted at a Veterans Administration Hospital and all patients signed consent forms.

Objectives

The primary study objective was to determine the maximum tolerated dose (MTD) of a continuous infusion of an escalating dose of cisplatin over 14 days administered concurrently with a fixed dose of oral etoposide for 14 days. The secondary objective was to assess the efficacy of this regimen in the treatment NSCLC.

Treatment plan

All patients received a fixed dose of oral etoposide of 50 mg/m^2 daily for 14 days. In addition, patients received cisplatin in an escalating dose level of 5, 6.5, 8, 9 and 10 mg/m^2/day continuously via an infuser for 14 days on an ambulatory basis. Three patients were entered at each dose level and if there was no more than one patient with grade III or IV toxicities encountered, then the next three patients were treated at the next higher dose level. However, if two or more patients developed grade III or IV toxicities, the following patients were treated at the next lower dose level, which was determined to be the maximum tolerated dose. Patients received up to 4 cycles of treatment unless tumor progression occurred. Administration of hematopoietic growth factors was not allowed.

Evaluation

Patients had weekly evaluation for toxicity and laboratory studies including complete blood count, electrolytes, blood urea nitrogen, creatinine, and magnesium. A computed tomography of the chest was performed at baseline and after the second and forth cycles to assess tumor response. Complete response was defined as resolution of all measurable and evaluable disease. Partial response was defined as $>50\%$ reduction in the tumor size. Stable disease was defined as changes of $<25\%$ of the tumor size and tumor progression was defined as an increase in the tumor size of $>25\%$. The WHO Toxicity Grading System was used to grade treatment-related toxicity.

Results

A total of 21 patients were enrolled in this study. All patients were men because the study was conducted in a Veteran Administration Hospital (Table 1). Three patients were treated at each level through level 4. Both patients treated at this dose level experienced multiple grade III/IV toxicities including renal, febrile neutropenia and gastrointestinal toxicities. Therefore, dose level 3 (cisplatin 8 mg/m^2/day) was determined to be the maximum tolerated dose. A total of 13 patients were enrolled at this dose level. Thirty-one cycles were administered at this dose level with a median of 2 cycles (1–4). Hematologic toxicities were the most common toxicities encountered including neutropenia, febrile neutropenia, thrombocytopenia and anemia (Table 2). One patient received a platelet transfusion and six patients received packed red blood cells. Patients with grade III/ IV hematologic toxicity were older patients as compared to those who had lesser hematologic toxicity (median age 72 versus 60 years). Grade IV renal toxicity was seem in only one patient, although 10 patients had grades I/II renal toxicity (Table 2). Seven patients had serum creatinine >2 mg/dl which was reversible in five patients. Other grade III/IV toxicities included hypomagnesemia ($n=1$), mucositis ($n=1$), and nausea and vomiting ($n=1$). There were no treatment-related deaths. One patient had a partial response and three patients had stable disease. Median survival was 5.5 months, and 1 and 2 year survival was 23 and 5%, respectively.

Table 1. Patient characteristics ($N=21$)

Median age (range)	64 (49–76) years
Gender	
male	21
female	0
Race	
white	15
African-American	6
PS	
1	8
2	13
Stage	
IIIB	8
IV	13
Histology	
adenocarcinoma	12
squamous	7
large cell	1
Poorly differentiated	1

Discussion

Treatment of NSCLC is a challenging task. Limited treatment options were available until recently.

Table 2. Chemotherapy-related grade III and IV toxicities

	Level I		Level II		Level III		Level IV	
	Patients	Cycles	Patients	Cycles	Patients [*N* (%)]	Cycles [*N* (%)]	Patients	Cycles
Total number per dose level	3	7	3	5	13	31	2	7
Leukopenia	0	0	0	0	5 (38)	8 (26)	2	5
Thrombocytopenia	0	0	0	0	3 (23)	6 (19)	2	4
Anemia	1	1	0	0	6 (46)	9 (29)	2	4
Renal	0	0	0	0	1 (8)	2 (6)	2	4
Hypomagnesemia	0	0	0	0	1 (8)	1 (3)	2	4
Nausea and vomiting	0	0	0	0	1 (8)	2 (6)	2	2
Mucositis	0	0	0	0	1 (8)	2 (6)	1	1

Cisplatin/etoposide was a widely used regimen in the US for many years and was shown to improve survival in advanced NSCLC patients.[13] This combination was generally given over 3–4 days every 3–4 weeks. The oral substitution of etoposide allowed greater flexibility in administration, less hospitalization and more acceptable toxicity.[14] This study is the first to combine both cisplatin and etoposide in a prolonged administration schedule. This study showed that the described regimen is feasible and reasonably well tolerated. However, the regimen administered as described in our study was not more effective than the combination administered over a shorter time period. The response rate was low (8%) and the median survival was lower than recently published studies.[19] The lack of efficacy of this regimen is not due to low dose density since the cumulative dose of cisplatin was 112 mg/m^2 and etoposide dose was 700 mg/m^2 per cycle. This lower response rate could be due to the small number of patients. On the other hand, it is possible that when given at lower doses, these drugs may lose their synergy or even may become antagonistic.[20] These findings also support the fact that higher doses of platinum may be required to attain a better response rate in NSCLC. In a study comparing weekly cisplatin dose with low daily cisplatin dose administered with radiation therapy for locally advanced NSCLC, the low daily dose resulted in better local disease control and survival. However, the low daily dose did not impact the time to progression of distant metastatic disease. Therefore, the low dose appeared effective as a radiosensitizer but not systemic therapy.[21] In another study, a higher dose of carboplatin administered every 4 weeks with weekly paclitaxel was found to be superior to weekly lower carboplatin with weekly paclitaxel in patients with advanced NSCLC.[22]

Furthermore, the impact of gender on treatment outcome is not known. In one study, prolonged oral etoposide was administered to 12 men and 13 women with NSCLC. Four of the five responders were women.[10] It is not clear whether male gender impacted treatment outcome in this study as all participants were males, but this remains a possibility. The toxicities encountered in this study were consistent with the known toxicities of this combination, which included renal failure, hypomagnesemia and hematologic toxicity. No new toxicity was identified and no toxicity-related death was encountered. It is not surprising that older people tend to have more toxicity, but the numbers are too small to draw definitive conclusions. Newer, more active and less toxic chemotherapeutic agents are currently available for the treatment of NSCLC.[23,24] However, due to cost-effectiveness, the combination of cisplatin and etoposide is still considered a treatment option for NSCLC.[6] Furthermore, the role of cisplatin in the treatment of lung cancer is enhanced by recent studies showing that cisplatin containing regimens remain essential in the management of NSCLC.

Conclusion

The prolonged administration of cisplatin/etoposide is feasible at the prescribed dose. Evaluation of this regimen should be done in the context of recent development of targeted therapy and other active agents in lung cancer. Prolonged Infusional cisplatin may prove to be beneficial in combination with other agents that have synergistic effects with platinum such as tirapazamine.

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