VINDESINE WITH CYCLOPHOSPHAMIDE-EPIRUBICIN-CISPLATIN IN THE TREATMENT LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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Abstract

Objective: To evaluate the addition of vindesine to a cyclophosphamide-epirubicin-cisplatin (CAP) regimen for treating the patients with locally advanced non-small cell lung cancer (NSCLC). Methods: From May 1994 to August 1998, 59 previously untreated patients with stage IIIa and IIIb non-small cell lung cancer were enrolled into this trial. Patients characteristics were the following: the median age was 52 years; the median performance status was 1; there were 19 stage IIIa and 40 stage IIIb; there were 47 adenocarcinoma, 10 squamous cell carcinoma and 2 large cell carcinoma. All patients were treated with vindesine (2 mg/m^2, on day 1 and day 8), cyclophosphamide (0.6/m^2, on day 1), epirubicin (40 mg/m^2, on day 1) and cisplatin (60 mg/m^2, on day 1) every 3 or 4 weeks. Results: Four achieved a complete response (6.8%), 29 achieved a partial response (49.2%), 15 had stable disease, and 10 had progressive disease. A clinical improvement was in 45 of 59 patients (76.3%). The most frequent major toxic effects were myelosuppression, nausea and vomiting. Conclusion: The vindesine with CAP regimen was active combination chemotherapy in patients with locally advanced NSCLC accompanied by the limited side effects.

Key words: Chemotherapy, Locally advanced NSCLC.

Lung cancer represents the leading cause of cancer deaths in human. Non-small cell lung cancer (NSCLC) accounts for about 75%–85% of all lung cancers and can be surgically resected in only 30%–40% of patients with limited disease.[1,2] The remaining patients, with locally advanced or metastatic disease (stages III and IV), are considered unresectable. The use of drug combinations in the treatment of unresectable NSCLC has been intensively investigated. The role of chemotherapy, however, remains controversial, especially considering the low survival rates obtained at 5 years of 10%–15%.[3,4]

Vindesine has been evaluated in patients previously untreated with chemotherapy, and an overall major response rate of 18% has been reported.[5,6] Cisplatin in combination with vinca alkaloids, vindesine or vinblastine, has been widely used for induction treatment of NSCLC since Gralla et al. first demonstrated a response rate of 43%.[7] Response rates of approximately 30% have been shown in advanced NSCLC using a combination of vindesine and cis-platin.[6,8] Combination regimens containing three drugs such as vindesine, mitomycin C and cisplatin (MVP regimen) or cyclophosphamide, epirubicin and cisplatin (CAP regimen) yielded objective responses ranging from 25%–60%.[9–12]

In view of superior anticancer activity of vindesine in non-small cell lung cancer, a trial of the four-agent combination of vindesine with CAP was undertaken in patients with locally advanced NSCLC. The purpose of this trial was to determine the major objective response rate for the regimen and to define the side effects of this treatment program.

MATERIALS AND METHODS

Patients for Entry on the Study

From May 1994 to August 1998, 59 previously untreated patients with histologically confirmed non-small cell lung cancer were entered. There were no concurrent radiotherapy protocols during the time of this investigation. All patients had stage IIIa and IIIb, according to the TNM classification.[13] Entry in the study required normal hematologic function, and measurable disease on a standard posteroanterior and

Accepted for publication: December 8, 1998
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lateral chest X-ray or computed tomography (CT), ultrasonography and/or physical examination.

Clinical Data

The characteristics of 59 patients are shown in Table 1. Most of the patients were male; the median age was 52 years; the median performance status was 1; there were 19 stage IIIa and 40 stage IIIb; there were 47 adenocarcinoma, 10 squamous cell carcinoma and 2 large cell carcinoma.

Table 1. Patients characteristics

Characteristics	No. of patients
Patients	59
Male/female	46/13
Age	
Median (range)	53 (41~66)
Histology	
Adenocarcinoma	47
Squamous cell carcinoma	10
Large cell carcinoma	2
Performance status	
0~1	41
2	17
Clinical stage	
IIIa	19
IIIb	40

Chemotherapy

All patients were treated with the combination of cyclophosphamide (600 mg/m^2 intravenously [IV] on day 1), epirubicin (40 mg/m^2 IV on day 1), cisplatin (60 mg/m^2 IV on day 1), and vindesine (2 mg/m^2 IV on day 1 and 8) with forced diuresis, repeated every 3 or 4 weeks. All patients received at least 2 or more cycles of chemotherapy.

Response Criteria

Response criteria are as follows: complete response (CR): complete disappearance of all objective evidence of tumor for at least 4 weeks; partial response (PR): decrease of 50% or more of the products of the two largest perpendicular diameters of measurable disease without evidence of new disease for at least 4 weeks; stable disease (SD): reduction of <50% or increase of <25% in tumor size; and progressive disease (PD): increase of 25% or appearance of new disease.

All patients were prospectively evaluated from the time of initiation of chemotherapy until objective documentation of disease progression. Response duration was calculated from the first day of treatment. Response ended on the date of the first objective measure of disease progression. Toxicity of treatment was graded according to WHO criteria.

RESULTS

The Objective Responses

As shown in Table 2, the over major objective response rate was 56% (33 responses among 59 patients). Four patients (6.8%) had complete response, 29 patients (49.2%) had partial response. Stable disease was observed in 25.4% (15/59) of the patients and disease progression occurred in 16.9% (10/59). A clinical improvement was in 45 of 59 patients (76.3%).

Table 2. The objective responses observed in 59 patients

Response	No. of patients (%)
Major response	33 (56)
Complete response	4 (6.8)
Partial response	29 (49.2)
No Major response	25 (42.4)
Stable disease	15 (25.4)
Disease progression	10 (16.9)

The Toxic-side Effects

The toxic effects observed during this trial are shown in Table 3. No patients died as a result of treatment. The most frequent major toxic effects were myelosuppression, nausea and vomiting. Fifty patients (84.7%) experienced myelosuppression, with 10.2% of patients having grade IV toxicity. Forty-nine patients (83.1%) suffered from nausea and vomiting, with 8.5% of patients having grade III toxicity. No life threatening infection or abnormal bleeding episode was documented. Nausea and vomiting were mild to moderate with no patient removed from study secondary to gastrointestinal toxicity. Cardiac toxicity and neurotoxicity were not documented in any patient.

DISCUSSION

Systemic chemotherapy for unresectable NSCLC has had a disappointing history. However response rates have been improved, with a large number of combination regimens, especially new drugs having been used. CAP is an useful regimen for some patients with NSCLC, with response rates ranging from 10% to 48%.[11,12] It was initially studied by Eagan et al. at the Mayo Clinic as a treatment regimen for NSCLC, where a 38% response rate was seen, with prolongation of survival in the responding patients. In follow-up studies, Eagan and co-workers used a higher cisplatin dose (60 mg/m^2) and observed a 48% regression rate. However no more improve-

ment of responses in the treatment of NSCLC have been seen with CAP. Vindesine is an effective agent in the treatment of NSCLC, it is a semisythetic vinca alkaloid derived from vinblastine and appears less neurologic toxicity than other vinca alkaloids. We used vindesine plus CAP to treat locally advanced NSCLC, the overall response rate was 56%. The results indicate it has significant antitumor activity in patients with NSCLC. In our trial, there was generally symptomatic improvement (76.3%).

Table 3. The toxicity of chemotherapy No. of cases (%)

Toxicity	I°	II°	III°	IV°
Leuocopenia	14 (23.7%)	16 (27.1%)	13 (23.7%)	6 (10.2%)
Anaemia	7 (11.9%)	6 (10.2%)	1 (1.7%)	
Thrombocytopenia	6 (10.2%)	5 (8.5%)	1 (1.7%)	
Nausea and vomiting	8 (13.6%)	36 (61.0%)	5 (8.5%)	
Hepatotoxicity (GPT)	4 (8.3%)			

At the time this study was designed, we reduced the doses of VDS from 3 mg/m^2 to 2 mg/m^2. Our experience with this drug strongly suggests it has severe myelosuppression, especially leuocopenia. Although patients of 84.7% still experienced myelosuppression with the dose reduction of VDS, most patients only had grade 1 or 2 toxicity. It did not affect our study and was well tolerated by our patients. Anaemia and thrombocytopenia were mild. In addition, neuorotoxicity was not documented. We think a reasonable dose of VDS appears to be 2 mg/m^2 weekly for two weeks per every cycle.

In conclusion, the vindesine with CAP regimen was active combination chemotherapy in patients with locally advanced NSCLC with limited side effects. Further evaluation of survival rates has to be performed continuously in the patients treated with this regimen. Finally, randomized trials are probably needed to compare the four-agent combination of cyclophosphamide, epirubicin, cisplatin plus vindesine to the three-drug regimen of mitomycin, cisplatin plus vindesine and to other active regimens.

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