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ORIGINAL ARTICLE

Effect of etoposide plus thalidomide as maintenance therapy on progression-free survival of elderly patients with advanced non-small cell lung cancer

Yanan Ge, Zhendong Zheng (Co-first author), Zhaozhe Liu, Jianing Qiu, Xiaodong Xie (✉)

Department of Oncology, General Hospital of Shenyang Military Region, Shenyang 110016, China

Abstract

Objective The aim of the study was to evaluate the efficacy and safety of etoposide plus thalidomide as maintenance therapy for elderly patients with advanced non-small cell lung cancer (NSCLC) without disease progression after first-line chemotherapy.

Methods After four to six cycles of platinum-based first-line therapy, 64 elderly patients with advanced NSCLC without disease progression who were treated in the General Hospital of Shenyang Military Region (China) from 2014 to 2016 were enrolled in this study. According to the different maintenance treatment methods, patients were divided as having received etoposide plus thalidomide therapy (treatment group, n = 32) and best supportive care (control group, n = 32). Disease control and progression-free survival (PFS) were compared between the two groups.

Results The recent curative effect objective response rates of the treatment group and the control group were 31.3% and 3.1%, respectively, and the disease control rates were 71.9% and 31.3%, respectively. The Kaplan-Meier survival curves of the two groups were significantly different (χ^2 = 26.532, P = 0.001). The median PFS for the treatment group and control group was 6.0 months [95% confidence interval (CI) = 4.3–7.9 months] and 3.2 months (95% CI = 2.6–3.8 months), respectively. The side effects in the treatment group included hematologic abnormalities, gastrointestinal toxicity, and impaired liver function, which were relieved after symptomatic support therapy and drug withdrawal.

Conclusion Etoposide plus thalidomide as maintenance therapy is associated with a significantly longer PFS with tolerable toxicity for elderly patients with advanced NSCLC.

Key words: etoposide; thalidomide; advanced non-small cell lung cancer (NSCLC); maintenance therapy

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Lung cancer is one of the most common causes of cancer death worldwide. It leads to more than 1 million deaths of patients each year. Non-small cell lung cancer (NSCLC) accounts for up to 85% of lung cancer cases, and 65%–70% of advanced stage cases are unsuitable for radical surgery or radiotherapy [1]. The median survival after currently used platinum-based first-line treatments is approximately 8 to 10 months [2]. With increasing life expectancy, there has been a notably elevated incidence of lung cancer worldwide, owing to the increasing cancer risk associated with age. Recently, the use of maintenance chemotherapy for NSCLC has been extensively investigated [3–4]. After four to six cycles of platinum-based first-line therapy, maintenance therapy for patients with NSCLC without disease progression can prolong the time to disease progression, improve quality of life, and ultimately prolong overall survival [5–6]. Etoposide is an important chemotherapeutic agent that is used to treat a wide spectrum of human cancers. The primary cytotoxic target for etoposide is topoisomerase II, a ubiquitous enzyme that regulates DNA by under- and overwinding to remove knots and tangles from the genome by generating transient double-stranded breaks in the double helix [7]. It has been used clinically for more than two decades and remains one of the most highly prescribed anticancer drugs in the world. Etoposide as maintenance chemotherapy conferred a benefit for survival in patients with NSCLC [8]. In recent years, etoposide combined with anti-angiogenic agents showed very promising activity for advanced NSCLC [7, 9].

Angiogenesis, the proliferation of new blood vessels, is necessary for tumors to grow. Thalidomide is an oral anti-

✉ Corresponding to: Xiaodong Xie. Email: doctor_xxd@163.com.

angiogenic agent, inhibiting angiogenesis mediated by vascular endothelial growth factor (VEGF), the activity of basic fibroblast growth factors, and microvessel formation in experimental models [10]. This anti-angiogenic activity is considered a contributing factor for its antitumor effects in multiple myeloma, although the mechanism is not yet fully understood. It also has a synergistic activity when combined with cytotoxic agents and potentially has wider therapeutic activity to small cell lung cancer (SCLC) [11].

We compared the effect between maintenance etoposide plus thalidomide and best supportive care in patients without disease progression after four to six cycles of platinum-based first-line chemotherapy.

Patients and methods

Patient selection

We reviewed the characteristics of patients diagnosed with advanced NSCLC between 2014 and 2016 in the General Hospital of Shenyang Military Region, China. Patients who met all the following inclusion criteria were enrolled in this trial: (1) age > 60 years, (2) histologically or cytologically proven advanced NSCLC, (3) detection of the wild-type *EGFR* gene, *ALK* gene fusion, or unknown gene mutation status, (4) four to six cycles of platinum-based first-line chemotherapy, (5) Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, (6) no disease progression after first-line chemotherapy, according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, (7) life expectancy of longer than 8 weeks, (8) no past tyrosine kinase inhibitors (TKI) treatment, and (9) adequate organ function [absolute neutrophil count (ANC) ≥ 1500 /mm^3, platelet count ≥ 100 000 /mm^3, hemoglobin ≥ 9.0 g/L, total bilirubin level ≤ 1.5 mg/dL, aminotransferase ≤ 2-fold upper limit of normal (ULN), creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 60 mL/min, and adequate renal function (calculated creatinine clearance > 50 mL/min)].

The exclusion criteria were as follows: (1) brain metastases, (2) diagnosis of synchronous malignant tumors, (3) unable to undergo follow-up, (4) severe bacterial infection, (5) intolerable adverse reaction to first-line chemotherapy, and (6) pregnancy or breastfeeding.

Treatments

Sixty-four elderly patients with advanced NSCLC according to the different maintenance treatment methods were divided as receiving etoposide plus thalidomide therapy (treatment group) and the best supportive care (control group). Etoposide was administered orally, 50 mg daily, from day 1 to 14, and the thalidomide starting dose was 100 mg/day during chemotherapy, and if tolerated, increased to 150 mg/day at the end of chemotherapy for three weeks. Dose modifications were made according to the drug instructions or the attending physician's judgment.

The recent curative effect objective response rate (ORR) [complete response (CR) + partial response (PR)] was defined as the proportion of patients whose tumors shrunk to a certain size and remained this way for a certain period (four weeks). Disease control rates (DCRs) included CR + PR + stable disease (SD). The long-term observation index, progression-free survival (PFS), was defined as the time from beginning maintenance treatment until disease progression. Tumor evaluation was performed using computed tomography one month after the start of medication and then every two months according to RECIST, version 1.1. Toxicity profiles were assessed and graded according to the Common Terminology Criteria for Adverse Events, version 3.0.

Statistical analysis

The primary endpoint was PFS. Secondary endpoints were tumor response (ORR and DCR) rates and toxicity. Clinicopathological characteristics were compared between the two groups by using the chi-square test. PFS was estimated using Kaplan-Meier curves and compared using the log-rank test. All statistical analyses were performed using SPSS 20.0 software (IBM SPSS, Armonk, NY, USA). *P* values less than 0.05 were considered statistically significant.

Results

Patient characteristics

A total of 64 cases were enrolled in the trial. According to the different maintenance treatment methods, 32 patients received etoposide plus thalidomide therapy (treatment group) and 32 received best supportive care (control group). In this trial, the smoking history, clinical stage, pathological type (squamous- or adenocarcinoma), ECOG score, and first-line chemotherapy curative effect had no statistical significance. Thus, all the patients were eligible for further analysis. At the initiation of therapy, the median age of the 64 eligible patients was 55 years. The baseline characteristics of the patients were balanced between the two groups (Table 1).

Efficacy assessment of maintenance therapy

During a median 12-month follow-up, 9 of the 32 patients in the treatment group and 22 of the 32 patients in the control group experienced progressive disease. The responses (ORR + DCR) were observed in a higher proportion of patients in the treatment group compared with those in the control group (Table 2).

A total of 64 patients with NSCLC were observed in

Table 1 Baseline characteristics of the patients in the two groups

Characteristic	Treatment (*n* = 32)	Control (*n* = 32)	χ^2	*P*
Gender			0.567	0.451
Male	19 (59.4%)	16 (50.0%)		
Female	13 (40.6%)	16 (50.0%)		
Smoking			0.259	0.611
Smoker	18 (56.3%)	20 (65.6%)		
Non-smoker	14 (43.8%)	12 (34.4%)		
ECOG			0.132	0.715
0–1	26 (81.3%)	27 (84.4.%)		
2	6 (18.8%)	5 (15.6%)		
Histology			0.804	0.669
Squamous	17 (53.1%)	19 (59.4%)		
Adeno	14 (43.8%)	11 (34.4%)		
Others	1 (3.1%)	2 (6.2%)		
Stage			0.259	0.611
IIIB	18 (56.3%)	20 (62.5%)		
IV	14 (43.8%)	12 (37.5%)		
After first-line			0.784	0.376
CR	0 (0)	0 (0)		
PR	9 (28.1%)	6 (18.8%)		
SD	23 (71.9%)	26 (81.2%)		

Table 2 Treatment response of patients in the two groups (*n*)

Groups	*n*	CR	PR	SD	PD	ORR (%)	DCR (%)
Treatment	32	3	7	13	9	10 (31.3%)	23 (71.9%)
Control	32	0	1	9	22	1 (3.1%)	10 (31.3%)
χ^2						1.010	0.784
P						0.315	0.252

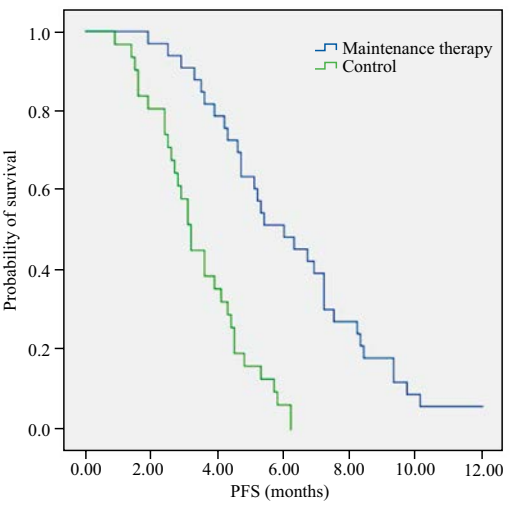

Fig. 1 PFS of the patients

our trial, and we compared the PFS between the two groups. We observed a trend of gained advantage in PFS in the treatment group compared with the control group. By the cutoff date, the median PFS in the treatment group was 6.0 months [95% confidence interval (CI) = 4.3–7.9 months], which was significantly longer than that in the control group (3.2 months, 95% CI = 2.6–3.8 months; χ^2=26.532, P = 0.001; Fig. 1).

Safety and tolerance

During our trial, we collected data regarding the severe adverse events. During maintenance therapy, the most frequently recorded grades 2–3 adverse events were hematologic abnormalities (20.3%), gastrointestinal toxicity (17.6%), and impaired liver function (9.7%). Etoposide was generally well tolerated. No grade 4 or higher adverse effects were recorded.

Discussion

Lung cancer is the principal cause of cancer-related death worldwide. The World Health Organization (WHO) classifies lung cancer into two subtypes: NSCLC and SCLC. NSCLC represents 85% of all lung cancer cases [1]. The first-line standard chemotherapy regimen for NSCLC is clear, but the effect has reached a plateau [12]. Maintenance therapy refers to the treatment period after completion of the initial standard chemotherapy for patients, and the purpose is to gain a maximum effect of tumor control after receiving continuous treatment. The treatment is not over until disease progression or intolerable toxicity occurs [5]. A non-randomized phase II study [9] have suggested that oral etoposide might be useful for treating extensive stage SCLC, especially in patients with advanced stage disease with poor prognosis. Patients aged > 65 years are likely to metabolize chemotherapeutic agents more slowly than younger patients, resulting in higher drug exposure levels and more serious adverse events [1]. Although pemetrexed is the recommended maintenance treatment for NSCLC, the need for intravenous therapy for long periods and the high cost are the reasons why most elderly patients with advanced lung cancer do not choose to receive pemetrexed. Etoposide has the advantages of being an orally administered agent with bioavailability. Etoposide involves topoisomerase II in the cell, inducing DNA double-strand breaks and early G2 phase blockage, but this effect disappears with reversal of etoposide [7]. The bioavailability of oral etoposide is 48%, and this may limit its clinical use as a palliative treatment, as some patients may be under-treated and others may have avoidable toxic effects. Single-agent oral etoposide as first-line chemotherapy and even maintenance therapy for SCLC prolongs the treatment time significantly [13]. A phase II trial found that the same dose of etoposide with sub-continuous administration had better effect than a single dose of therapy, and etoposide in the second-line

chemotherapy for refractory and relapsed patients could acquire 46% of the ORR [14]. As such, etoposide in our trial was administered in 50-mg doses, per os, on days 1–15 for three weeks. Cancers rely on angiogenesis for their growth and dissemination. Thalidomide has been shown to significantly inhibit tumor growth in mice injected with NSCLC cell lines, and early phase trial in humans has also indicated that this therapy was well tolerated and merited further investigation [15]. Although the precise antiangiogenic or resistance mechanisms of thalidomide are not yet fully understood, the possible reason is that tumor blood vasculature is already established in advanced NSCLC, VEGF may be superfluous, and angiogenesis is affected by other proangiogenic factors [16]. Other advantages of thalidomide are convenient oral administration and lower costs, and potentially beneficial anticachexia and immunomodulatory properties.

We believe that patients with a tumor response or stable disease might have more opportunity to benefit from agents such as etoposide and thalidomide. Morover, the new treatment is combined with standard chemotherapy in all patients at the start of chemotherapy, and then continues as maintenance. The PARAMOUNT study was the first proof of the effectiveness of maintenance therapy for advanced NSCLC [17]. The ASCO meeting in 2011 reported that the DCRs were 71.8% and 59.6%, respectively ($P = 0.009$) for the maintenance and placebo groups. PFS in the maintenance therapy group was 3.9 months, significantly longer than 2.6 months in the placebo group.

In our trial, the ORRs with etoposide plus thalidomide and best support were 31.3% and 3.1% ($\chi^2 = 0.010$, $P = 0.315$), and the DCRs were 71.9% and 31.3% ($\chi^2 = 0.784$, $P = 0.252$), respectively. The differences in ORRs and DCRs were not significant ($P > 0.05$) between the two groups. The median PFS with etoposide plus thalidomide and best support was 6.0 months (95% CI = 4.3–7.9 months) and 3.2 months (95% CI = 2.6–3.8 months), respectively. There was a significant difference in the PFS in the two groups ($P < 0.05$). Our trial indicated that etoposide plus thalidomide as maintenance therapy for advanced NSCLC after first-line chemotherapy significantly prolonged the PFS, with tolerable adverse reactions and convenient oral administration.

In conclusion, our data showed that etoposide plus thalidomide as maintenance therapy was associated with a PFS benefit in elderly patients with advanced NSCLC.

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Conflicts of interest

The authors indicated no potential conflicts of interest.

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