

RESEARCH ARTICLE

Clinical Investigation of Efficacy of Albumin Bound Paclitaxel plus Platinum Compounds as First-line Chemotherapy for Stage III/IV Squamous Non-small Cell Lung Cancer

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Abstract

Objective: To observe the efficacy and toxicity of nanoparticle albumin bound paclitaxel (nab-paclitaxel) plus platinum agent (cisplatin or carboplatin) as first line treatment for stage III/IV squamous non-small-cell lung cancer (NSCLC). **Methods:** Forty chemotherapy naive patients with stage III/IV squamous NSCLC received nab-paclitaxel 125 mg/m² on day 1 and day 8, cisplatin 75 mg/m² on day 1, carboplatin area under the concentration-time curve of 5 (AUC=5) on day 1. One cycle of treatment was 3 weeks, and at least two were completed in each case. **Results:** Of the 40 patients who participated in the study, 25 achieved partial responses (PR), 12 reached a stage of stable disease (SD), and 3 suffered progressive disease (PD). The overall response rate (ORR) was 62.5% and the disease control rate (DCR) was 92.5%. Of the 20 patients without surgery or radiotherapy, 10 achieved PR, 7 reached a stage of SD, and 3 PD. The ORR was 50.0% and the DCR was 85.0%. The median progression-free survival time (PFS) of patients without surgery or radiotherapy was 5.0 months. Of the 20 patients receiving surgery or radiotherapy, 15 had PR and 5 p had SD, with an ORR of 75.0% and a DCR of 85.0%. Specifically, the DPP arm demonstrated a significantly higher ORR than the CBP arm (100% vs 54.5%, $P < 0.05$). Common treatment related adverse events were myelosuppression, gastrointestinal response, baldness and neurotoxicity, most of which were grade 1 to 2. **Conclusion:** Nab-paclitaxel plus platinum agent (cisplatin or carboplatin) is effective as a first-line chemotherapy for stage III/IV squamous NSCLC, and its adverse effects are tolerable.

Keywords: Albumin bound paclitaxel - cisplatin - carboplatin - squamous non-small cell lung cancer

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Introduction

Recently, great progression have been made on the research of pulmonary adenocarcinoma. Pemetrexed, a third-generation chemotherapeutic agent, has showed its favorable efficacy and tolerable toxicity both in first-line, second-line and maintenance treatment of pulmonary adenocarcinoma (Hanna et al., 2004; Scagliotti et al., 2008; Ciuleanu et al., 2009), so the combination chemotherapy of pemetrexed and platinum compounds is recommended as first-line standard therapy for advanced non-small cell lung cancer (NSCLC) by NCCN. Targeted drugs, such as bevacizumab, combined with chemotherapy, are also quite effective treatment for pulmonary adenocarcinoma (Barlesi et al., 2013). There are various therapeutic treatments of targeted EGFR-TKI inhibitor owing to the 50~60% EGFR mutation rate in Asiatic pulmonary adenocarcinoma patients (Shi et al., 2014). In contrast, there is no breakthrough in treatment of pulmonary adenocarcinoma and the treatment options are also limited. Nanoparticle albumin bound paclitaxel

(nab-paclitaxel), a new type of paclitaxel praeparatum, has many advantages like high efficiency, low toxicity and convenience. Our department applied nanoparticle albumin bound paclitaxel (nab-paclitaxel) combined platinum agents (cisplatin, DPP or carboplatin, CBP) as first-line treatment in 40 lung squamous carcinoma patients between February, 2011 to October, 2013, and the results are as follows.

Materials and Methods

Clinical data

Eligible adults had histologically/cytologically confirmed nonresectable stage III or IV squamous carcinoma from February 2011 to October 2013. All patients were naive cases, including 36 males and 4 females, aged between 30 to 79 years, the median age was 61. 26 cases in stage III including 24 cases in III A period and 2 cases in III B ; 14 cases in IV ; 19 cases receiving nanoparticle albumin bound paclitaxel plus cisplatin, 21 cases in combination with carboplatin. All patients were

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Table 1. Baseline Characteristics of 40 Patients

Clinical feature	N	Percentage
Sex		
Male	36	90.0%
Female	4	10.0%
Age		
Median	61	
<65	27	67.5%
≥65	13	32.5%
ECOG scores		
0~1	37	92.5%
1-3	3	7.5%
Clinical stage		
Stage III	26	65.0%
Stage III A	24	60.0%
Stage III B	2	5.0%
Stage IV	14	35.00%
Therapeutic schedule		
nab-PC+DDP	19	47.5%
nab-PC+CBP	21	52.5%

confirmed the presence of measurable lesions by CT scan and the Eastern Cooperative Oncology Group (ECOG) score was 0~2, and a life expectancy of more than 3 months. Their routine blood test and electrocardiogram were generally normal before treatment, meanwhile liver and kidney functions ≤ 1.5 times the normal range. All patients signed consent form before treatment. Table 1 gives general situation of 40 cases.

Methods

Albumin-bound paclitaxel was used at a dose of 125 mg/m² (injection for over 30 minutes). The drug was administered on a day 1 and day 8 schedule every three weeks. Cisplatin was administered at 75 mg/m² on day 1 every three weeks. Carboplatin was administered at an area under the curve (AUC) of 6 calculated according to the Calvert formula on day 1 every three weeks. The efficacy was evaluated every two cycles. Hematologic and imaging examinations were routinely performed during the medication. The original protocol would be kept for 2~4 cycles if it was effective.

Assessment of efficacy and adverse reactions

The objective efficacy was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The observation indicators included complete remission (CR), partial response (PR), stable disease (SD), disease progression (PD), objective response rate (ORR), and disease control rate (DCR). Progression-free survival (PFS) is defined as the time from first medication to the first objective progression of disease. The evaluation of adverse reactions was based on the NCI Common Toxicity Criteria (CTC) Version 3.0.

Statistics analysis

Statistical analysis was done by SPSS 13.0 software. Correlation between clinical features and curative effects was valued by using χ^2 test. PFS was analyzed using Kaplan-Meier methods. A value of $p < 0.05$ was considered to be statistically significant.

Table 2. Clinical Feature and Correlation of Curative Effect the of Nab-paclitaxel Plus Platinum Agent as First Line Treatment on Lung Squamous Carcinoma

Clinical feature	N	PR	SD	PD	ORR	P	DCR	P
Sex						0.586		0.548
Male	36	23	10	3	63.9%		91.7%	
Female	4	2	2	0	50.0%		100%	
Age						0.433		0.974
<65	27	18	7	2	69.2%		92.5%	
≥65	13	7	5	1	53.8%		92.3%	
Clinical stage						0.608		0.950
Stage III	26	17	7	2	65.4%		92.3%	
Stage IV	14	8	5	1	57.1%		92.9%	
Therapeutic schedule						0.165		0.489
Nab-PC+DDP	19	14	3	2	73.7%		89.5%	
Nab-PC+CBP	21	11	9	1	52.4%		95.2%	
ECOG scores						0.278		0.077
0~1	37	24	11	2	64.9%		94.6%	
2	3	1	1	1	33.3%		66.7%	

Table 3. Analysis of Curative Effect in Subgroup without Surgery or Radiotherapy

Group without surgery or radiotherapy	N	PR	SD	PD	ORR	P	DCR	P	PFS(m)
Stage III	7	2	3	2	28.6%	0.160	71.4%	0.212	4.3
Stage IV	13	8	4	1	61.5%		92.3%		5.3
Group plus DDP	10	5	3	2	50.0%	1.000	80.0%	0.531	4.5
Group plus CBP	10	5	4	1	50.0%		90.0%		5.4
Total	20	10	7	3	50.0%		85.0%		5.0

Results

Short-term efficacy

All patients were eligible for efficacy evaluation. A total of 137 cycles of treatment was delivered overall, with a median number of cycles per patient of 3 (range, 1 to 6). There were 25 cases of PR (62.5%), 12 cases of SD (30.0%), 3 cases of PD (7.5%), and ORR 62.5% (25/40), DCR 92.5% (37/40). There were 14 cases of PR (73.7%), 3 cases of SD (15.8%), 2 cases of PD (10.5%), ORR 73.7% (14/19), DCR 89.5% (17/19) in the group which 19 patients received treatment plus cisplatin. There were 11 cases of PR (62.5%), 9 cases of SD (30.0%), 1 case of PD (7.5%), ORR 52.4% (11/21), DCR 95.2% (20/21) in the group which 21 patients received treatment plus carboplatin. 15 patients received radiotherapy and 4 patients received surgery after the 26 patients on stage III received 2~3 cycles of chemotherapy. 7 patients gave up radiotherapy or surgery treatment because of their poor pulmonary function, multiple primary diseases and intolerance in which there were 2 cases of PR (28.6%), 3 cases of SD (42.9%) and 2 cases of PD (28.6%). 1 case with metastasis of sinistro-adrenal gland in the 14 patients on stage IV was evaluated PR and received treatment of surgery according to multi-disciplinary assessment after 2~3 cycles of chemotherapy. There were 8 cases of PR (61.5%), 4 cases of SD (30.8%) and 1 case of PD (7.7%) in the 13 patients who neither received surgery nor radiotherapy. In the whole group, 20 patients neither received surgery nor radiotherapy, in which there were 15 cases of PR (75.0%), 5 cases of SD (25.0%) and 0 case of PD, ORR 75.0% (15/20), DCR 100% (20/20); 9 cases received treatment plus cisplatin in which there were 9 cases of PR (100%), 0 case of SD, 0 case of PD, ORR

Table 4. Analysis of Curative Effect in Subgroup with Surgery or Radiotherapy

Group with surgery or radiotherapy	N	PR	SD	PD	ORR	P
Stage III	19	14	5	0	73.7%	0.544
Stage IV	1	1	0	0	100%	
Group plus DDP	9	9	0	0	100%	0.038
Group plus CBP	11	6	5	0	54.5%	
Total	20	15	5	0	100%	

Table 5. Adverse Effects of Nab-paclitaxel Plus Platinum Agent

Adverse effects	WHO grade		
	I/II (%)	III (%)	IV (%)
Leukopenia	14 (35.0%)	8 (20.0%)	2 (5.0%)
Thrombocytopenia	5 (12.5%)	2 (5.0%)	2 (5.0%)
Baldness	15 (37.5%)	9 (22.5%)	0 (0.0%)
Neurotoxicity	20 (50.0%)	3 (7.5%)	0 (0.0%)
Nauseated, vomiting	21 (52.5%)	4 (12.5%)	0 (0.0%)
Liver function damage	4 (10.0%)	0 (0.0%)	0 (0.0%)
Renal function damage	2 (5.0%)	0 (0.0%)	0 (0.0%)

100.0% (9/9), DCR 100% (9/9) and 11 cases received treatment plus carboplatin in which there were 6 cases of PR (54.5%), 5 cases of SD (45.5%), 0 case of PD, ORR 54.5% (6/11), DCR 100% (11/11) (Table 2~5).

Survival analysis

We kept following up by clinic service or telephone from the beginning of treatment to October 31st, 2013. PFS of the 20 patients who had no surgery or radiotherapy was 1.4~17.9 months, and median-PFS was 5 months in which PFS of patients on stage III was 4.3 months and 5.3 of stage IV. PFS of patients received cisplatin was 4.5 months and that received carboplatin was 5.4 months. The PFS of 19 cases on stage III and 1 case on stage IV was censored values because of their treatment of surgery or radiotherapy (Table 4, Figure 1~3).

Adverse effects

Adverse effects of nanoparticle albumin bound paclitaxel (nab-paclitaxel) plus platinum agent (cisplatin or carboplatin) was myelosuppression, gastrointestinal response, badness and neurotoxicity. I/II degree leukopenia were 14 (35.0%), III degree 8 (20.0%) and IV degree 2 (5.0%). I/II degree decreased platelet count were 5 (12.5%), III degree 9 (22.5%) and IV degree 2 (5.0%). I/II degree hair loss were 15 (37.5%) and III degree were 9 (22.5%). I/II degree periphery neurotoxicity were 20 (50.0%) and III degree were 3 (7.5%). I/II degree gastrointestinal reaction were 21 (52.5%) and III degree were 4 (10.0%). I/II degree liver damage were 4 (10.0%). I/II degree kidney damage were 2 (5.0%).

Discussion

Paclitaxel, with broad-spectrum antitumor activity, is approved for the treatment of advanced non-small-cell lung cancer (Li et al., 2013; Natukula et al., 2013; Gurses et al., 2013; Ozdemir et al., 2013; Cui et al., 2014). With the vector of albumin, it can reduce risk of hypersensitivity

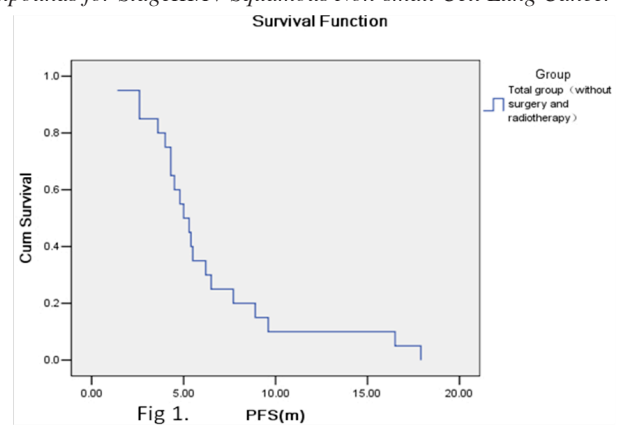


Figure 1. Progression-free Survival (PFS) of Allpatients without Surgery or Radiotherapy. The median PFS were 5 months

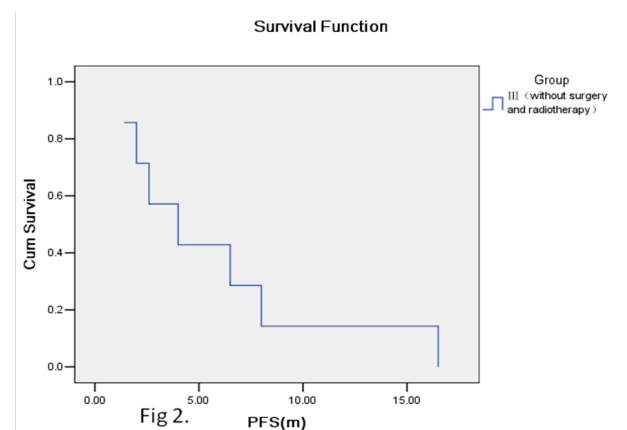


Figure 2. Progression-free Survival (PFS) of Stage III Patients without Surgery or Radiotherapy. The median PFS were 4.3 months

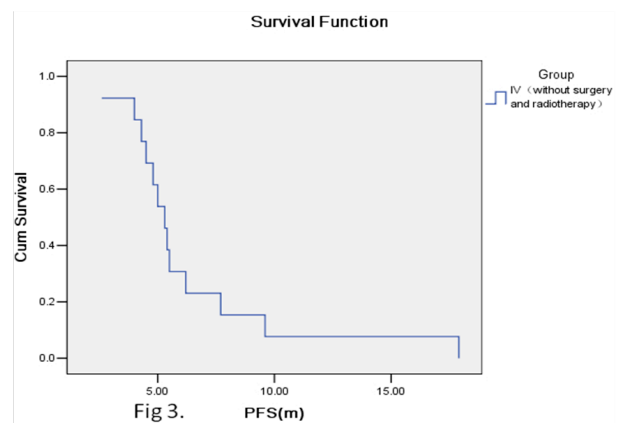


Figure 3. Progression-free Survival (PFS) of Stage IV Patients without Surgery or Radiotherapy. The median PFS were 5.3 months

reactions and blood toxicity induced by organic solvent. It exploits the natural properties of album into increase of uptake and causes accumulation of paclitaxel in the tumor through gp 60-mediated endothelial transcytosis (Aapro et al., 2008), and interaction with the album in-binding protein SPARC (secreted protein, acidic and rich in cysteine). Nab-paclitaxel has greater antitumor activity with increased intratumoral concentrations (Trieu et al., 2006; Desai et al., 2009). Socinski et al. (2013) conducted a major international multicenter randomized phase III

clinical study of nab-paclitaxel compared solvent-based paclitaxel. 1052 patients in the phase III/IV NSCLC was enrolled and randomly assigned to carboplatin and either nab-paclitaxel or solvent-based paclitaxel for the first-line treatment. the ORR was higher with nab-*P/C* versus sb-*P/C* (34% versus 25%, $P=0.005$). further histologic subgroup analysis for squamous histology indicated the ORR was 67% higher with nab-paclitaxel (41%) than solvent-based paclitaxel (24%). There was no survival difference between nab-paclitaxel and solvent-based paclitaxel. This is the best efficacy of lung squamous carcinoma data reported in literatures. According to the analysis by investigator, the treatment with nab-paclitaxel demonstrated greater short-term efficacy with potentially increasing uptake and accumulation of paclitaxel in the tumor through gp60-CAV1 mediated endothelial transcytosis induced by abnormal higher expressions of CAV-1.

In this study we enrolled 40 patients with lung squamous carcinoma took nab-paclitaxel combined with cisplatin or carboplatin. The ORR was 62.5% and the DCR was 92.5%. The ORR was up to 73.7% in patients with nab-paclitaxel combined with cisplatin, and was better than the data reported in the literature. In Socinski's study, the ORR was 44.4% in lung squamous carcinoma patients. The treatment of nab-paclitaxel showed better effective compared with solvent-based paclitaxel in western countries, for instance, the efficacy of the general third generation platinum-based two drugs combination chemotherapy was 17% to 22% (Schiller et al., 2002). The reason for the efficacy in this study was superior to the results reported maybe related to the race. The previous research revealed the efficacy of chemotherapy or targeted therapy of East Asian patients was better than that on Western patients. The median PFS in the patients without surgery or radiotherapy was 5 months, the phase III patients 4.3 months and the phase IV patients 5.3 months. The reason for the higher efficacy seemingly did not translate to the median PFS extension compared with 5.6 months median PFS reported in Socinski's study in lung squamous carcinoma, it is probably attributed to that the patients abandon the initial therapy without disease progression, such as, turned to surgery or radiotherapy. The continuity of chemotherapy was effected because that the patients who was older, with poor lung functions and suffering diseases could not receive the further surgery or radiotherapy. the prolong of median PFS was effected with some patients who was in phase IV and discontinued the therapy because of the economy or un-tolerance adverse drug reaction. The ORR in the treatment combined with cisplatin (100%) was tremendously higher than that with carboplatin (63.6%) in the patients with surgery or radiotherapy. The treatment of nab-paclitaxel plus platinum-based chemotherapy may be a optimal protocol for the patients with good physical situation and tolerance because that it could alleviate the tumor load rapidly and strengthen the efficacy of local tumor especially to make a chance of the surgery for the potential patients and maximized reduction of the volume of the tumor.

Finally, the nab-PC showed a better safety and tolerability with neutropenia, sensory nerve toxicity, the

incidence of myalgia obviously reduced, except anemia and thrombocytopenia increased. Nab-PC was approved chemotherapy agent for the patients with advanced or metastatic NSCLC in the first-line treatment.

In general, the most common AEs were myelosuppression, gastrointestinal reaction and baldness, and secondary AEs neurovirulence. The most AEs were I/II degree, except 4 myelosuppression with IV degree which eased after symptomatic therapy. And there was no treatment-related deaths occurred. In sum, the nab-paclitaxel combined with cisplatin or carboplatin has a good tolerance for lung squamous carcinoma with the first-line treatment.

In summary, the combination of nab-paclitaxel and cisplatin or carboplatin indicated better short-term efficacy, less AEs, and well tolerated. The protocol of nab-paclitaxel combined with platinum-based make a chance for the treatment of the lung squamous carcinoma especially multidisciplinary synthetic therapy of locally advanced lung squamous carcinoma to improve the efficacy and prolong survival with currently less selectable chemotherapy and no precise efficacy of targeted-therapy. This study was a retrospective analysis with small sample size. The efficacy and toxicity of the treatment of nab-paclitaxel combined with platinum-based for Asian or Chinese patients needed a prospective, large sample, multi-center clinical study.

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