

Phase II Study of a Bi-Weekly Chemotherapy Regimen of Combined Liposomal Paclitaxel and Nedaplatin for the Treatment of Advanced Squamous Cell Lung Cancer



Wei-Ze Lv^{*,1}, Zhong Lin^{*,1}, Si-Yang Wang[†],
Bao-Jun Lv[‡], Zhi-Hui Wang^{*}, Mei Xiao^{*}, Xiao-Lu Xu^{*}
and Pei-Jian Peng^{*}

^{*}Department of Medical Oncology, The Fifth Affiliated Hospital of Sun-Yat-Sen University, Zhuhai, Guangdong Province, People's Republic of China; [†]Department of Radiation Oncology, The Fifth Affiliated Hospital of Sun-Yat-Sen University, Zhuhai, Guangdong Province, People's Republic of China; [‡]Department of Surgical Oncology, The Fifth Affiliated Hospital of Sun-Yat-Sen University, Zhuhai, Guangdong Province, People's Republic of China

Abstract

The platinum-based, two-drug, 3-week regimen is currently the main first-line chemotherapy program for the treatment of advanced squamous cell lung cancer. The aim of this phase II clinical study was to evaluate the efficacy and adverse events of the bi-weekly program of liposomal paclitaxel combined with nedaplatin as a first-line treatment for advanced squamous cell lung cancer. A total of 52 cases of advanced squamous cell lung cancer were included in this phase II clinical trial. Patients received intravenous infusion of liposomal paclitaxel (100 mg/m²) and nedaplatin (50 mg/m²) on days 1 and 15 of a 4-week cycle. Each patient received two to six cycles of chemotherapy, consistent with the regimen of combined liposomal paclitaxel and nedaplatin. The total effective rate of this chemotherapy program was 37.5%. The median progression-free survival time was 8.5 months (95% confidence interval: 7.8–9.2). The median survival time was 16 months (95% confidence interval: 14.1–17.9). The main adverse event was myelosuppression. Grade 3 leukopenia was noted in seven patients (13.5%), and no grade 4 leukopenia was observed. Grade 3 anemia was noted in four patients (7.7%), and no grade 4 anemia was observed. In addition, no grade 2 or higher thrombocytopenia and no grade 3 or 4 non-bone marrow toxicity was detected. The bi-weekly program of liposomal paclitaxel combined with nedaplatin is effective for the treatment of advanced squamous cell lung cancer, with high safety and few adverse events. However, additional studies are warranted to confirm these results. The trial was registered under the number ChiCTR-OIN-17011423.

Translational Oncology (2019) 12, 656–660

Introduction

The global incidence of lung cancer has been increasing rapidly in recent years [1]. The numbers of new lung cancer cases and deaths caused by lung cancer in China in 2015 were 733,300 and 610,200, respectively [2]. Therefore, lung cancer has become a serious threat to health. Approximately more than 50% of lung cancer patients cannot be treated by surgery due to advanced disease at the time of diagnosis [3,4]. Squamous cell lung cancer accounts for 25–30% of non-small cell lung cancer (NSCLC). Although significant progress has been made in the treatment of non-squamous NSCLC, progress in advanced squamous cell lung cancer remains limited [5]. Platinum-based regimens, including third-generation chemotherapeutic agents such as paclitaxel, gemcitabine, vinorelbine, and docetaxel, are

considered standard first-line treatments for advanced squamous cell lung cancer patients. The median survival of these patients is roughly 10–12 months [5,6].

Address all correspondence to: Pei-Jian Peng, MD, Department of Medical Oncology, The Fifth Affiliated Hospital of Sun-Yat-Sen University, 52 Mei Hua Road East, Zhuhai 519000, Guangdong Province, People's Republic of China.

E-mail: pengjian@163.com

¹Wei-Ze Lv and Zhong Lin contributed equally to this work.

Received 6 December 2018; Revised 30 January 2019; Accepted 30 January 2019

© 2019 The Authors. Published by Elsevier Inc. on behalf of Neoplasia Press, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). 1936-5233/19

<https://doi.org/10.1016/j.tranon.2019.01.008>

New third-generation chemotherapeutic agents combined with platinum have similar therapeutic effects. However, these chemotherapeutic agents may cause severe bone marrow suppression [6–8]. Paclitaxel is a compound with a taxane ring extracted and purified from *Taxus* bark [9]. Paclitaxel inhibits mitosis and tumor cell proliferation by binding to cell microtubules and inhibiting microtubule depolymerisation [10]. However, paclitaxel, which is difficult to dissolve in water, is typically prepared with polyoxyethylene castor oil for injection, which can induce histamine release and allergies and/or systemic muscle and joint pain [7,8]. Liposomes are novel drug carriers that encapsulate insoluble paclitaxel in the liposome phospholipid bilayer to improve its solubility. Indeed, liposomal paclitaxel significantly increased the concentration of chemotherapeutic agents within the tumor *in vivo*, which improved the efficacy and reduced the side effects of anti-tumor drugs [11,12]. In addition, clinical studies have shown that liposomal paclitaxel has similar efficacy and less toxicity compared with paclitaxel for the treatment of NSCLC [13–15].

Nedaplatin, a second-generation platinum complex, does not exhibit cross-resistance with traditional cisplatin or carboplatin [16]. In a previous clinical study, nedaplatin achieved a similar overall response rate (ORR) and overall survival (OS) rate as did cisplatin for the treatment of advanced NSCLC. The disease control rate (DCR) of nedaplatin combined with third-generation chemotherapeutic agents for advanced NSCLC reached 48.6–95.2% [17,18]. Regarding squamous cell lung cancer, the combination of nedaplatin and docetaxel exhibited significantly improved efficacy and survival benefits compared with cisplatin combined with docetaxel [19].

It has been confirmed in colorectal cancer [20], castration-resistant advanced prostate cancer [21], and gastric cancer that the bi-weekly chemotherapy program is effective with minimal toxicity [22]. However, the efficacy and side effects of bi-weekly chemotherapy have not been investigated extensively in NSCLC. To our knowledge, a bi-weekly regimen of combined liposomal paclitaxel and nedaplatin has not been investigated as first-line chemotherapy for advanced NSCLC. Based on the promising results mentioned above, we designed a phase II trial to evaluate the efficacy and side effects of the bi-weekly program of liposomal paclitaxel combined with nedaplatin for the treatment of advanced squamous cell lung cancer.

Materials and Methods

Patients and Inclusion Criteria

A total of 52 advanced squamous cell lung cancer patients who met the following inclusion criteria were included in the present prospective study: 1) histological or cytological diagnosis of stage IIIb–IV lung squamous cell carcinoma with measurable tumor lesions not treated with chemotherapy; 2) performance status (PS) score of 0–2 based on the Eastern Cooperative Oncology Group scoring system; 3) >3 months of expected survival; 4) >18 years of age; 5) absolute neutrophil count $\geq 1.5 \times 10^9/L$, hemoglobin level ≥ 80 g/L, platelet count $\geq 75 \times 10^9/L$, total bilirubin level $\leq 1.5 \times$ upper limit of normal (ULN), aspartic acid and alanine aminotransferase levels $\leq 2.5 \times$ ULN, and serum creatinine level $\leq 1.5 \times$ ULN; 6) no brain metastasis; and 7) newly diagnosed cases. This study was reviewed and approved by the Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University. Informed consent was obtained from all included patients. The trial was registered under the number ChiCTR-OIN-17011423.

The exclusion criteria were (1) breastfeeding and/or pregnant patients; (2) systematic diseases including acute infections, major cardiovascular disease such as myocardial infarction over the past 1 year, serious liver diseases, serious kidney diseases and metabolic disorders; (3) other malignant tumors during the last 5 years, except for malignant tumors that can be treated by radical resection, including *in situ* cervical cancer, basal or squamous cell skin cancer, breast *in situ* intraductal carcinoma and localized prostate cancer; and (4) viral diseases that may be transmitted *via* the blood or other body fluids, such as human immunodeficiency virus, hepatitis B or hepatitis C.

Chemotherapy

The chemotherapy program consisted of two to six cycles, with each cycle lasting for 28 days. Intravenous infusion of liposomal paclitaxel (100 mg/m²) and nedaplatin (50 mg/m²) was conducted on days 1 and 15 of each cycle. Patients quit the chemotherapy program if intolerable side effects or rapid disease progression occurred. The 52 advanced squamous cell lung cancer patients completed a total of 186 chemotherapy cycles, and an average of 3.58 cycles was completed per patient.

To reduce the risk of allergic reactions to liposomal paclitaxel, all patients received intravenous infusion of dexamethasone (10 mg) and cimetidine (400 mg) and intramuscular injection of diphenhydramine (40 mg) prior to administration of liposomal paclitaxel. Conventional antiemetic therapy was conducted before and after chemotherapy. Granulocyte colony stimulating factor was used when appropriate.

Evaluation of Efficacy and Side-Effects

The primary objective of this clinical trial was to evaluate the response rate, progression-free survival (PFS), and toxicity of the combination chemotherapy regimen of liposomal paclitaxel and nedaplatin for advanced squamous cell lung cancer. Secondary objective was overall survival. Imaging examinations and tumor lesion measurements were performed every two cycles. A blood test, liver and kidney function evaluations, and electrocardiogram were conducted before and after each cycle to evaluate the side effects of the chemotherapy program. Efficacy was evaluated on the basis of the Response Evaluation Criteria in Solid Tumors 1.1 criteria and classified into four grades as follows: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria (version 3.0) before each treatment cycle. Patients quit the chemotherapy program if the chemotherapy was delayed for >3 weeks due to toxicity.

Dose Adjustment

The chemotherapy dose was adjusted when grade 3 or higher toxicity was observed. The chemotherapy dose was reduced by 20% or 40% when grade 3 or 4 toxicity occurred, respectively. Patients quit the chemotherapy program if the chemotherapy dose needed to be reduced by >40%.

Statistical Analyses

Statistical analyses were conducted using the SPSS 17.0 software package. OS, ORR, TTP, and toxicity were assessed for all patients. All patients received at least two cycles of toxicity assessment. The Kaplan–Meier method was used to analyze the survival data.

Results

Patient Characteristics

A total of 52 patients with advanced squamous cell lung cancer hospitalized between July 2013 and June 2016 were enrolled in this

Table 1. Patient characteristics

Characteristics	Patient number	Percentage (%)
Total	52	100
Sex		
Male	37	71.2
Female	15	28.8
Age(years)		
Median	61	N/A
Range	32–75	N/A
ECOG performance status		
0	8	15.4
1	34	65.4
2	10	19.2
Staging		
IIIb	6	11.5
IV	46	88.5
Smoking exposure		
Smoking	44	84.6
Never smoking	8	15.4

ECOG: Eastern Cooperative Oncology Group; N/A: not applicable.

prospective study. Patient characteristics are listed in Table 1. The ages of the 52 patients (37 males and 15 females) ranged from 32 to 75 years. The median age was 61 years. The PS scores were 0–1 and 2 for 42 and 10 patients, respectively. Six and 46 patients were diagnosed with stage IIIb and IV advanced squamous cell lung cancer, respectively. Of the 52 patients, 44 were smokers (including ex-smokers).

Efficacy

All 52 patients completed more than two chemotherapy cycles. Efficacy evaluation was successfully conducted for all patients. Of the 52 patients, 20, 21, and 11 exhibited PR, SD, and PD after chemotherapy, respectively. A CR was not observed in any of the 52 patients. The total effective rate (CR + PR) and the disease control rate (CR + PR + SD) were 38.5% and 78.9%, respectively. All patients were followed up after the completion of chemotherapy. The median PFS was 8.5 months (95% confidence interval [CI]: 7.8–9.2) (Figure 1) and the median survival 16 months (95% CI: 14.1–17.9) (Figure 2).

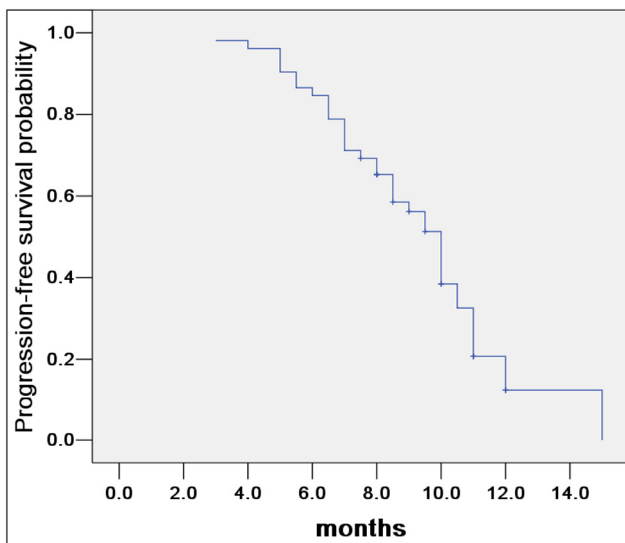


Figure 1. Kaplan–Meier curve of progression-free survival.

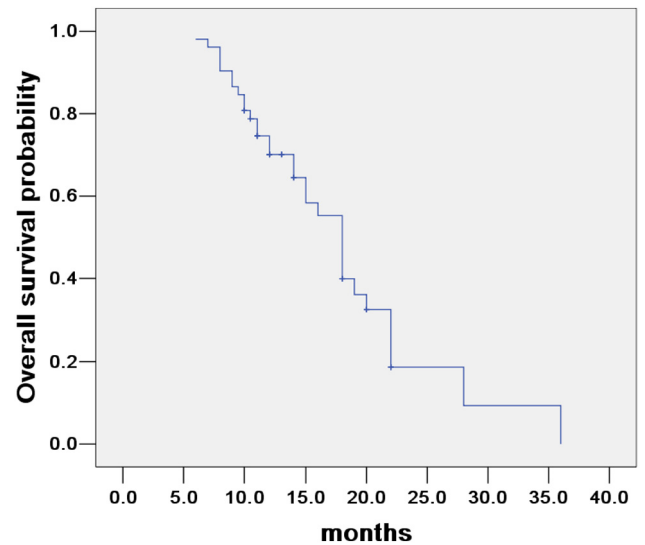


Figure 2. Kaplan–Meier curve of overall survival.

Side-Effects

Most of the side effects observed were reversible. The most common side effect was myelosuppression. Grade 3 neutropenia was noted in seven patients (13.5%), whereas no patient had grade 4 neutropenia. Grade 3 anemia was noted in four patients (7.7%), whereas no patient had grade 4 anemia. No patient had grade 2 or higher thrombocytopenia, and no grade 3 or 4 non-bone marrow toxicity was observed. Grade 1 allergic reactions induced by nedaplatin were found in two cases. Other side effects were mild and tolerable. No treatment-related death was reported (Table 2).

Discussion

As a novel chemotherapeutic agent, paclitaxel has become one of the most effective drugs for the treatment of advanced NSCLC. The effective rates of single-agent chemotherapy using paclitaxel and combination chemotherapy using paclitaxel and cisplatin are 21–24% and 42%, respectively [8,10,23,24]. While paclitaxel has been widely used as an effective drug for the treatment of NSCLC, severe allergic reactions and peripheral nerve toxicity limit the clinical application of paclitaxel in chemotherapy [9,10].

Liposomes are lipid spheres composed of phospholipids. As a novel drug carrier, liposomes can reduce drug toxicity, alter the dynamic properties and tissue distribution of drugs, and decrease the drug

Table 2. Treatment-related adverse events (n = 52)

Side effects	NCI-CTCAE grade n(% of patients)			
	1	2	3	4
Neutropenia	16(30.8%)	7(13.5%)	7(13.5%)	0
Thrombocytopenia	8(15.4%)	5(9.6%)	0	0
anemia	10(19.2%)	6(11.5%)	4(7.7%)	0
Nausea/vomiting	15(28.8%)	8(15.4%)	0	0
Allergic reactions	2(3.8%)	0	0	0
Liver damage	5(9.6%)	0	0	0
Renal impairment	2(3.8%)	0	0	0
Hair loss	14(26.9%)	5(9.6%)	0	0
neurotoxicity	11(21.2%)	6(11.5%)	0	0

NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Event.

elimination rate to prolong the drug action time [11,12]. Thus, liposomal adriamycin and liposomal cisplatin have been used clinically [25,26]. Liposomes can significantly improve the solubility of paclitaxel in water and reduce drug toxicity, especially allergic reactions. In addition, liposomal paclitaxel exhibits sustained-release effects *in vivo* and causes minimal side effects, such as bone marrow suppression and liver toxicity [11,12]. Moreover, liposomal paclitaxel is at least as effective as paclitaxel for advanced NSCLC [13–15]. Nedaplatin is a second-generation platinum drug that was approved in China in 2001. After nedaplatin enters cells, the bond between alcoholic oxygen and platinum on the glycolate breaks to release the platinum. Free platinum in cells binds to water to produce a number of ions that bind to DNA and inhibit DNA replication and tumor cell growth [19]. Nedaplatin has shown significant activity against advanced NSCLC (especially squamous cell lung cancer) and causes less renal and gastrointestinal toxicities than does cisplatin [17–19,27]. Recently, another phase 3 trial has been reported that nedaplatin offers advantage over cisplatin in patients with advanced squamous cell lung cancer [28]. Therefore, a combination of liposomal paclitaxel and nedaplatin to treat advanced squamous cell lung cancer is very rational.

Liposomal paclitaxel has not been widely used in the clinic in most countries. Therefore, few studies have reported on the combination of liposomal paclitaxel and nedaplatin for the treatment of advanced NSCLC. However, the 3-week chemotherapy regimen of liposomal paclitaxel combined with nedaplatin has been widely used for the treatment of NSCLC (especially squamous cell lung cancer) in China. The reported efficiency of the 3-week chemotherapy regimen of liposomal paclitaxel plus nedaplatin for the treatment of NSCLC reached up to 40%, and the major side effect was bone marrow suppression. Based on promising results obtained from the bi-weekly chemotherapy regimens [29–31] and the minimal side effects of the 3-week chemotherapy regimen, we hypothesized that bi-weekly administration of liposomal paclitaxel and nedaplatin may be effective and better tolerated than the 3-week regimen in patients with advanced NSCLC. To test this hypothesis, we designed this prospective trial.

A multi-centre phase II trial conducted in Greece revealed that the efficacy of a bi-weekly regimen of docetaxel combined with gemcitabine for first-line treatment of advanced NSCLC was similar to those of other 3-week regimens, with high safety and tolerability. Among the 31 patients evaluated, 16 cases of PR (16/31, 55.2%) and 3 cases of SD (3/31, 10.3%) were reported. The median TTP was 3 months (range 0–12 months), with a mean OS of 10 months (range 3–31 months) [31]. In a randomized, open-label, phase 3 study, Shukuya et al. reported that first-line treatment with nedaplatin and docetaxel exhibited significantly better efficacy and survival benefits than did cisplatin combined with docetaxel in patients with squamous cell lung carcinoma [19]. The ORR was 56%, with a median PFS of 4.9 months and a median OS of 13.6 months, in the nedaplatin group. In the present study, the response rate, median PFS, and median OS of the bi-weekly chemotherapy regimen of liposomal paclitaxel combined with nedaplatin for the treatment of advanced squamous cell lung cancer were 38.5%, 8.5 months, and 16 months, respectively, which are similar to those of several currently used first-line chemotherapy programs for NSCLC. While this regimen resulted in a lower response rate, it exhibited improved survival benefits. However, we are unable to conclude whether bi-weekly liposomal paclitaxel combined with nedaplatin is indeed superior or comparable

to other bi-weekly or 3-week regimens as a first-line treatment in terms of efficacy. Thus, further prospective randomized studies are warranted.

In the present study, liposomes were used as paclitaxel carriers for the treatment of advanced squamous cell lung cancer and were found to reduce the allergic reactions induced by polyoxyethylene castor oil in patients. No allergic reactions induced by liposomal paclitaxel were observed, suggesting that liposomal paclitaxel is relatively safe for lung cancer chemotherapy. No renal toxicity was observed in any patient. We also observed a low incidence of nausea and vomiting (grade 2 or 3), significantly lower than the incidences reported previously for cisplatin combination chemotherapy [11,15,19]. The main adverse event of this combination chemotherapy program was myelosuppression. All patients tolerated the adverse effects, including hematological toxicity. Thus, these toxicities were mild and well-tolerated.

In summary, our results suggest that the bi-weekly chemotherapy regimen of liposomal paclitaxel combined with nedaplatin is useful for the treatment of advanced squamous cell lung cancer with higher safety and clinical tolerability. Less non-hematologic and hematologic toxicities were observed in this bi-weekly chemotherapy regimen (compared with platinum-based, two-drug, 3-week regimen). Bi-weekly chemotherapy regimen of liposomal paclitaxel combined with nedaplatin could be a new first line treatment option for advanced squamous cell lung cancer patients. However, there are a number of limitations to this study, such as its small sample size, lack of a control group, and limited clinical data. Therefore, multi-centre, randomized, phase 3 studies with larger sample sizes are needed to further investigate the efficacy and side effects of bi-weekly chemotherapy using liposomal paclitaxel combined with nedaplatin compared with platinum-based, two-drug, 3-week regimen for the treatment of advanced squamous cell lung cancer.

Authors' Contributions

P. J. P. and W. Z. L. were responsible for study design. P. J. P., W. Z. L., and Z. L. drafted the manuscript. S. Y. W. and B. J. L. participated in the data interpretation. Z. H. W., X. M. and X. L. X. participated in the data collection and analysis. All authors have read and approved the final manuscript.

Disclosure Statement

The authors have no conflict of interest.

References

- [1] Siegel RL, Miller KD, and Jemal A (2016). Cancer statistics, 2016. *CA Cancer J Clin* **66**(1), 7–30.
- [2] Chen WQ, Zheng RS, Baade PD, Zhang SW, Zeng HM, Bray F, Jemal A, Yu XQ, and He J (2016). Cancer statistics in China, 2015. *CA Cancer J Clin* **66**(2), 115–132.
- [3] Heist RS and Engelman JA (2012). SnapShot: non-small cell lung cancer. *Cancer Cell* **21**(3), 448.e2.
- [4] Reck M, Popat S, Reinmuth N, De Ruyscher D, Kerr KM, and Peters S (2014). Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* **25**(Suppl. 3), iii27–iii39.
- [5] Socinski MA, Obasaju C, Gandara D, Hirsch FR, Bonomi P, Bunn P, Kim ES, Langer CJ, Natale RB, and Novello S, et al (2016). Clinicopathologic Features of Advanced Squamous NSCLC. *J Thorac Oncol* **11**(9), 1411–1422.
- [6] Thatcher N, Hirsch FR, Luft AV, Szczesna A, Ciuleanu TE, Dediu M, Ramlau R, Galulin RK, Bálint B, and Losonczy G, et al (2015). Nectinmab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. *Lancet Oncol* **16**(7), 763–774.

- [7] Davidoff AJ, Tang M, Seal B, and Edelman MJ (2010). Chemotherapy and survival benefit in elderly patients with advanced non-small-cell lung cancer. *J Clin Oncol* **28**(13), 2191–2197.
- [8] Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu JM, and Johnson DH (2002). Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* **346**(2), 92–98.
- [9] Wani MC, Taylor HL, Wall ME, Coggon P, and McPhail AT (1971). Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*. *J Am Chem Soc* **93**(9), 2325–2327.
- [10] Rowinsky EK, Cazenave LA, and Donehower RC (1990). Taxol: a novel investigational antimicrotubule agent. *J Natl Cancer Inst* **82**(15), 1247–1259.
- [11] Koudelka S, Turanek-Knotigová P, Masek J, Korvasová Z, Skrabalová M, Plocková J, Bartheldyová E, and Turánek J (2010). Liposomes with high encapsulation capacity for paclitaxel: Preparation, characterisation and in vivo anticancer effect. *J Pharm Sci* **99**(5), 2309–2319.
- [12] Yoshizawa Y, Kono Y, Ogawara K, Kimura T, and Higaki K (2011). PEG liposomalization of paclitaxel improved its in vivo disposition and anti-tumor efficacy. *Int J Pharm* **412**(1–2), 132–141.
- [13] Wang XH, Zhou JC, Wang YS, Zhu ZY, Lu Y, Wei YQ, and Chen LJ (2010). A phase I clinical and pharmacokinetic study of paclitaxel liposome infused in non-small cell lung cancer patients with malignant pleural effusions. *Eur J Cancer* **46**(8), 1474–1480.
- [14] Wang HY and Zhang XR (2014). Comparison of efficacy and safety between liposome-paclitaxel injection plus carboplatin and paclitaxel plus carboplatin as first line treatment in advanced non-small cell lung cancer. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* **36**(3), 305–308.
- [15] Yang XJ, Zhang H, Nong JY, Wang JH, Li X, Zhang Q, Wang QH, Gao Y, and Zhang SC (2012). A randomized trial of liposomal paclitaxel plus cisplatin as first-line therapy for advanced non-small cell lung cancer. *Zhongguo Fei Ai Za Zhi* **15**(4), 208–212.
- [16] Alberto ME, Lucas MF, Pavelka M, and Russo N (2009). The second-generation anticancer drug Nedaplatin: a theoretical investigation on the hydrolysis mechanism. *J Phys Chem B* **113**(43), 14473–14479.
- [17] Hirose T, Sugiyama T, Kusumoto S, Shirai T, Nakashima M, Yamaoka T, Okuda K, Ogura K, Ohnishi T, and Ohmori T, et al (2009). Phase II study of the combination of nedaplatin and weekly paclitaxel in patients with advanced non-small cell lung cancer. *Anticancer Res* **29**(5), 1733–1738.
- [18] Li CH, Liu MY, Liu W, Li DD, and Cai L (2014). Randomized control study of nedaplatin or cisplatin concomitant with other chemotherapy in the treatment of advanced non-small cell lung cancer. *Asian Pac J Cancer Prev* **15**(2), 731–736.
- [19] Shukuya T, Yamanaka T, Seto T, Daga H, Goto K, Saka H, Sugawara S, Takahashi T, Yokota S, and Kaneda H, et al (2015). Nedaplatin plus docetaxel versus cisplatin plus docetaxel for advanced or relapsed squamous cell carcinoma of the lung (WJOG5208L): a randomised, open-label, phase 3 trial. *Lancet Oncol* **16**(16), 1630–1638.
- [20] Shitara K, Yuki S, Yoshida M, Takahari D, Utsunomiya S, Yokota T, Sato Y, Inaba Y, Tajika M, and Kawai H, et al (2012). Phase II study of combination chemotherapy with biweekly cetuximab and irinotecan for wild-type KRAS metastatic colorectal cancer refractory to irinotecan, oxaliplatin, and fluoropyrimidines. *Invest New Drugs* **30**(2), 787–793.
- [21] Kellokumpu-Lehtinen PL, Harmenberg U, Joensuu T, McDermott R, Hervonen P, Ginman C, Luukkka M, Nyandoto P, Hemminki A, and Nilsson S, et al (2013). 2-weekly versus 3-weekly docetaxel to treat castration-resistant advanced prostate cancer: a randomised, phase 3 trial. *Lancet Oncol* **14**(2), 117–124.
- [22] Felici A, Carlini P, Ruggeri EM, Gamucci T, Pollera CF, De Marco S, Fariello AM, Moscetti L, Gelibter A, and Adami E, et al (2006). Bi-weekly chemotherapy with cisplatin, epirubicin, folinic acid and 5-fluorouracil continuous infusion plus g-csf in advanced gastric cancer: a multicentric phase II study. *Cancer Chemother Pharmacol* **57**(1), 59–64.
- [23] Lustberg MB and Edelman MJ (2007). Optimal duration of chemotherapy in advanced non-small cell lung cancer. *Curr Treat Options Oncol* **8**(1), 38–46.
- [24] Scagliotti G (2007). Optimizing chemotherapy for patients with advanced non-small cell lung cancer. *J Thorac Oncol* **2**(Suppl. 2), S86–S91.
- [25] Stathopoulos GP, Antoniou D, Dimitroulis J, Michalopoulou P, Bastas A, Marosis K, Stathopoulos J, Provata A, Yiamboudakis P, and Veldekis D, et al (2010). Liposomal cisplatin combined with paclitaxel versus cisplatin and paclitaxel in non-small-cell lung cancer: a randomized phase III multicenter trial. *Ann Oncol* **21**(11), 2227–2232.
- [26] Straubinger RM, Arnold RD, Zhou R, Mazurchuk R, and Slack JE (2004). Antivascular and antitumor activities of liposome-associated drugs. *Anticancer Res* **24**(2A), 397–404.
- [27] Xu RH, Guang ZZ, Jiang WQ, Huang H, Hu XH, Xie WM, Li XG, Liu YL, Pan LX, and Dai AD, et al (2002). Phase II clinical trial of nedaplatin in advanced non-small cell lung cancer. *Ai Zheng* **21**(12), 1354–1358.
- [28] Lu S, Chen ZW, Hu CP, Zhang J, Chen Y, Song Y, Zhao Q, Fan Y, Wu G, and Ma ZY, et al (2018). Nedaplatin plus docetaxel versus cisplatin plus docetaxel as first-line chemotherapy for advanced squamous cell carcinoma of the lung—a multicenter, open-label, randomized, phase III trial. *J Thorac Oncol* **13**(11), 1743–1749.
- [29] Kosmas C, Tsavaris N, Syrigos K, Koutras A, Tsakonas G, Makatsoris T, Mylonakis N, Karabelis A, Stathopoulos GP, and Kalofonos HP (2007). A phase I-II study of bi-weekly gemcitabine and irinotecan as second-line chemotherapy in non-small cell lung cancer after prior taxane + platinum-based regimens. *Cancer Chemother Pharmacol* **59**(1), 51–59.
- [30] Saitoh J, Saito Y, Kazumoto T, Kudo S, Yoshida D, Ichikawa A, Sakai H, Kurimoto F, Kato S, and Shibuya K (2012). Concurrent chemoradiotherapy followed by consolidation chemotherapy with bi-weekly docetaxel and carboplatin for stage III unresectable, non-small-cell lung cancer: clinical application of a protocol used in a previous phase II study. *Int J Radiat Oncol Biol Phys* **82**(5), 1791–1796.
- [31] Syrigos KN, Danno I, Dionellis G, Bofos I, Alamara C, Dimakou E, Stratakou G, and Papiris S (2005). Bi-weekly administration of docetaxel and gemcitabine as first-line therapy for non-small cell lung cancer: a phase II study. *Anticancer Res* **25**(5), 3489–3493.