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ORIGINAL ARTICLE

Pharmacokinetics and safety of lobaplatin plus etoposide in Chinese men older than 65 years with extensive-stage small cell lung cancer: a phase II clinical trial

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Abstract

Purpose This phase II, multicenter, single arm clinical study was first performed to evaluate the therapeutic efficacy and safety of the regimen—a combination of lobaplatin (LBP) and etoposide (VP-16)—and investigate the pharmacokinetics of LBP in Chinese men older than 65 years with extensive-stage small cell lung cancer (SCLC).

Methods Patients older than 65 were treated with the combination of LBP and VP-16 for 4–6 cycles through intravenous drip. The initial dose of VP-16 was 100 mg/m^2/day for d1-d3 in each 21-day cycle, while LBP was administrated for d1 in each cycle based on creatinine clearance (Ccr), 20 mg/m^2 for Ccr < 60 mL/min; 25 mg/m^2 for 60 ≤ Ccr < 80 mL/min and 30 mg/m^2 for Ccr ≥ 80 mL/min. Efficacy, safety and pharmacokinetics were evaluated to confirm the therapeutic effect.

Results Thirteen elderly patients were enrolled and three patients were discontinued. The median progress-free survival was 129 days and the median overall survival was 238 days, which caused a significantly prolonged survival rate of 38.5% and a higher disease control rate of 80%. Most frequent adverse events were mild to moderate containing leukopenia, neutropenia, anemia, nausea and anorexia. Pharmacokinetic analysis revealed that there is no significant difference between LP-D1 and LP-D2 at the same dosage level. With the dosage increasing, the elimination clearance showed a slowing tendency, especially for 30 mg/m^2 group.

Conclusions LBP (20, 25, 30 mg/m^2) in combination with VP-16 (100 mg/m^2) could inhibit the elderly SCLC disease process, prolong their survival time and reduce adverse reactions via preliminary assessment and provide guidance for further investigation.

Keywords Lobaplatin · Small cell lung cancer · Pharmacokinetic · Elderly · Phase II trial

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Introduction

Small cell lung cancer (SCLC), a neuroendocrine cancer that accounts for 15–20% of lung cancers, is pathologically, molecularly, and clinically different from other lung cancers [1]. Aggressive behaviors, rapid proliferation and sensitiveness to chemotherapy are all regarded as the characteristics of SCLC.

With the aging population in China and the increasing prevalence of SCLC, 25–40% of patients suffering SCLC are the elderly population, a special group with particularly concerned. It is expected to increase because of their deteriorative kidney function causing an incomplete drug metabolism [2–4]. Researches [5, 6] have shown that the weight of kidney will decrease by 10–20% for people aged 40–80 years owning to the nephrons reduction in number and size aspects and the renal blood flow of the 65 year olds is only 40–50% of that in young people whose reduce by 1.5–1.9% per year.

For the treatment of SCLC, the current chemotherapy is a combination of platinum agent and etoposide [7–9]. Reduced or split doses of EP regimen, consisting of cisplatin (DDP) and etoposide (VP-16), is considered as an international standard for the first-line elderly SCLC treatment. However, it still exist diverse toxicity of DDP and severely limits its clinical application, especially for the aged patients who have poor medical condition. Carboplatin (CBP) plus etoposide is also a standard treatment and generally applied to elderly SCLC patients in virtue of its hypotoxicity. While, it has been reported that Lobaplatin (LBP, 1,2-diaminomethyl–cyclobutane-platinum (II)-lactate), a newly third-generation platinum-based agent, can be used instead of DDP or CBP for extensive-stage SCLC because of its higher security and stronger antitumor effect. It was primarily used for the treatment of SCLC, advanced breast cancer and chronic myeloid leukemia [10–12]. Clinical observations suggest that compared with EP regimen, EL (LBP combined VP-16) regimen has an equivalent antitumor efficacy for SCLC, exhibits a milder gastrointestinal response, ototoxicity, nephrotoxicity and possesses a better patient tolerance [13–15]. However, the efficacy of EL regimen by an individualized administration in Chinese elderly patients with extensive-stage SCLC has not been sufficiently evaluated.

Additionally, LBP is a mixture that consists of two diastereoisomers (LP-D1, RRS configuration and LP-D2, SSS configuration) by 1:1 equal proportion (Fig. 1) and exerts antitumor effect by blocking DNA replication and transcription to inhibit the expression of gene in tumor cell [16]. Although processing similar chemical structures, two diastereoisomers are likely to have different behaviors on the aspects of toxicity, pharmacokinetics and pharmacodynamics in vivo, especially for those aged patients. The total concentration of LBP has been previously quantified by atomic absorption spectrometry (AAS) without the separation of LP-D1 and LP-D2 [17]. And we also found that more attention was focused on the non-small cell lung cancer (NSCLC) or SCLC which related to rats or adults [18–20]. Besides, more current articles were published respecting the antitumor efficacy of LBP [21–23], and it results in a paucity of similar researches till now, which focus on both an individualized clinical therapeutic evaluation and the pharmacokinetic studies about the forms of LP-D1, LP-D2, LPB as well as platinum in elderly presenting extensive stage SCLC.

According to the current situation of SCLC treatment mentioned above, a phase II, multicenter, single arm clinical study was first proposed to mainly evaluate the therapeutic efficacy and safety of the EL regimen and investigate the pharmacokinetic behavior of different forms of LBP in 13 Chinese men older than 65 years with extensive-stage SCLC. Pharmacokinetic studies were applied to the aged patients by a dose escalation way to assess whether two diastereoisomers would show different elimination rates and the pharmacokinetic behaviors of other LBP forms were also studied. Furthermore, the therapeutic efficacy and safety of EL regimen were evaluated in this article. To sum up, this study is of great significance for further clinical therapeutic investigation regarding LBP combined VP-16 and provided a new platform for the pharmacokinetic study and individualized administration for Chinese male patients over 65 years with extensive-stage SCLC.

Methods

Study design

A multi-center phase II clinical study with prospective, single-arm open, pharmacokinetic, and dose escalation regimen was designed for 13 SCLC male patients with the age over 65. This clinical study was divided into the following three parts: screening period, treatment period, and follow-up period.

Patient selection

The screening criteria were as follows: (a) age ≥ 65 years old containing male and female; (b) SCLC is diagnosed by the evaluation of histopathology or cytology; (c) clinical stage of the subjects should belong to extensive stage (exclude the cases of metastases only pleural effusion); (d) subjects should have no chemotherapy history; (e) the function of bone marrow, liver, kidney and coagulation are normal; (f) the subjects who have palliative radiotherapy or surgical treatment stop the therapy for more than 2 weeks; (g) subjects who have measurable lesions (non-radiation site) (RECIST evaluation: the diameter of common CT is not

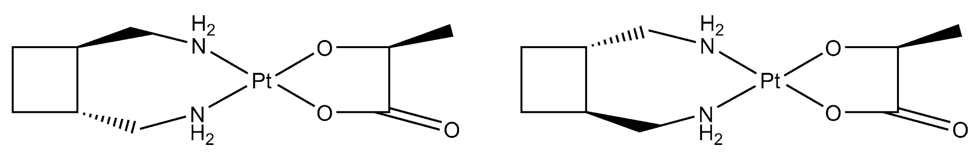

Fig. 1 Chemical structures of two diastereoisomers: LP-D1 and LP-D2

less than 20 mm or the diameter of spiral CT is not less than 10 mm, and the longest diameter is more than twice the thickness of the scanning layer); (h) physical condition score ECOG PS: 0–1; (i) the survival time of subjects was expected at least 3 months; (j) subjects should be contraceptive, and non-lactating during the study or after the treatment within 6 months.

All eligible subjects entered this study had signed an informed consent before.

Treatment

LBP plus VP-16 was regarded as the treatment schedule and called as EL regimen in this clinical research. The initial dose of VP-16 for all 13 subjects was administered at a dosage of 100 mg/m^2 dissolved in 250 mL normal saline on the first three consecutive days of each cycle for intravenous drip administration. It should be used strictly in accordance with the drug instructions to prevent allergies. The initial dose of LBP was stratified into the following three groups on the basis of Ccr which represents their different kidney function levels: (a) patient whose Ccr < 60 mL/min, 20 mg/m^2 LBP dissolved in 250–500 mL normal saline was given on the first day of each cycle for intravenous constant infusion for 2 h; (b) patient whose 60 mL/min ≤ Ccr < 80 mL/min, 25 mg/m^2 LBP was administered in the same way as above; (c) patient whose Ccr ≥ 80 mL/min, 30 mg/m^2 LBP was given for the first day of each cycle. Clinical efficacy, adverse effects and several responses to the administration such as progressive disease (PD), partial response (PR), progress-free survival (PFS), and overall survival (OS) were evaluated after 4–6 cycles of EL regimen.

Pharmacokinetic sampling and analyzing

Five milliliter blood samples were collected and placed in a previously numbered anticoagulant tube coated with heparin sodium at 0, 0.2, 0.5, 1, 2, 4, 6, 8, 12 and 24 h after administration. One milliliter blood samples were taken to the frozen tubes which was numbered before, and 4 mL remaining blood samples were immediately centrifuged with the speed of 3000–4000 rpm for 5–10 min at room temperature and all the collected plasma samples were stored at − 20 °C until use. Besides, all frozen samples used for analysis should be defrosted and equilibrate at room temperature.

The separation of two diastereoisomers was carried on a rapid and high-sensitive supercritical fluid chromatography-tandem mass spectrometry (SFC-MS/MS) system (Waters, USA) with a multiple reaction monitoring (MRM). This Acquity UPC^2 SFC system has a tandem quadrupole mass spectrometer (Waters, USA) interfaced by electrospray ionization (ESI) in the mode of positive ion. The chromatographic separation was performed on a Chiralcel OZ-RH (150 mm × 4.6 mm, 5μm) column with 10 μl injection and the column oven was maintained at 55 °C. The mobile phase composed of CO_2 (purity ≥ 99.99%) and methanol (including 2.5 mM ammonium acetate and 0.05% ammonia) was pumped at a flow rate of 2.0 mL/min with an isocratic elution program (60:40, v/v). MRM was utilized to determine the transitions of protonated ion $[M+H]^+$ at *m/z* 398.20 → 291.10 for LBP and *m/z* 256.30 → 167.10 for IS (Diazepam). Compared with the published methods [24], this new method was equipped with the superiorities of less analysis time, lower low limit of quantitation (LLOQ) and wider linear range. The quantitative analysis of total platinum and combined LBP was determined by inductively coupled plasma mass spectrometry (ICP-MS) and high-performance liquid chromatography (HPLC–MS), respectively.

The total concentration of platinum was determined by ICP-MS (NexION 300D, PerkinElmer, USA) for quantitative analysis. 400 μl human whole blood was placed into 10 mL centrifuge tube with 3.6 mL aqueous solution concluding 0.65% HNO_3, 0.1% Triton and 0.5% Butanol. The mixture was centrifuged at the speed of 3500 rpm for 10 min after vortex for 1 min. 20 μl supernatant was taken into ICP-MS for analysis.

HPLC–MS was utilized on the detection of combined LBP concentration. 100 μl plasma sample was taken with the additional solution of 100 μl acetonitrile–water (50:50, v/v) and 400 μl ice acetonitrile. The mixture was vortexed for 45s and centrifuged at 15,000 rpm for 5 min at 4 °C. Twenty microliter supernatant was analyzed by HPLC–MS.

The analytical data was captured and processed by Analyst Software (Masslynx 4.2, Waters, USA). And the analysis of plasma samples was met the relevant requirements of the Technical Guidelines for the Study of Bioavailability and Bioequivalence of Chemicals in Chemical Preparations (March 2005) promulgated by China CFDA. Parameters of pharmacokinetic (PK) study were calculated using the software DAS 3.0 (Drug and Statistics Software, Mathematical Pharmacology Professional Committee of China, Shanghai, China).

Follow-up studies

Four to six cycles are recommended for the above schedule, and it will stop until progressive disease (PD), or the patients cannot tolerate the toxicity. If the patient does not have PD after 6 cycles, the administration will be terminated. Efficacy, safety, pharmacokinetics, and follow-up studies are regularly assessed during the trial. Follow-up period was assessed every 2 months for the efficacy and safety until PD, or the study was completed.

We used the RECIST version 1.1 to evaluate the efficacy of the subjects. The specific criteria for evaluated indicators were listed as follows: complete remission (CR): all target lesions disappeared. The shortest diameter of all pathological lymph nodes is < 10mm; partial remission (PR): compared to the baseline, the sum of the measured diameters of all target lesions was shortened by ≥ 30%; disease progression (PD): compared to the smallest sum of the measured diameters, the sum of the measured diameters of all target lesions is increased by ≥ 20%, and the absolute value of the sum is increased by ≥ 5 mm, or new lesions appear; stable disease (SD): tumors do not meet PD or PR criteria due to enlargement or reduction; objective effectiveness (ORR): the ratio of the best overall response in each treatment group to CR and PR (CR + PR) subjects; disease control rate (DCR): refers to the proportion of subjects with the best overall outcome determined in each treatment group as CR, PR, or SD (CR + PR + SD).

Statistical analyzes

Progression-free survival was defined as the interval between the date of initiation of EL regimen and that of disease progression or death. Overall survival was defined as the date of initiation of EL regimen to the date of death or the last follow-up. Survival curves were plotted using the Kaplan–Meier method. No inferential statistics were possible due to small sample size.

Results

Patients

A total of 13 eligible subjects were enrolled and received the treatment in three groups according to the creatinine clearance level. Two patients were terminated due to a screening failure of the treatment protocol diversion and one patient was discontinued because of an economic reason. The first patient signed informed consent on 15 December 2015, and the last patient completed the study on 17 July 2017. Ten patients among the entire groups of study subjects were received a completed trial. The detailed characteristic information for 13 eligible subjects in this study is listed in Table 1.

Table 1 The characteristic information for the eligible subjects in this study

Characteristics	No. of subjects
Subjects, *n*	13
Mean age (range), years	68 (65–73)
Male/female, *n*	13/0
Smoking history(%), *n*	11 (84.6)
Mean weight, kg (SD)	62.5 (8.8)
Mean BMI, kg/m^2 (SD)	22.9 (2.0)
Mean creatinine clearance (%), *n*	
Ccr < 60 mL/min	5 (38.5)
60 ≤ Ccr < 80 mL/min	5 (38.5)
Ccr ≥ 80 mL/min	3 (23)
Previous treatment, *n*	0
Histological diagnosis(%), *n*	13 (100)
Extensive state of SCLC(%), *n*	13 (100)
Starting dose, *n*	
20 mg/m^2	5
25 mg/m^2	5
30 mg/m^2	3

Adverse events

A total 89 cases of adverse events (AE) were collected from thirteen subjects. Among them, 76 cases (85.4%) were belonged to hematological toxicities, and the major toxicities: anemia, neutropenia, leukopenia account for 33.7%, 22.5%, and 21.3%, respectively. These toxicities were common adverse reactions of platinum drugs. However, most of them (56 cases, 73.7%) were classified into grade I–II according to the WHO criteria. Additionally, some non-hematological toxicity (14.6%) such as fever, nausea and itchy skin were also monitored and they all belonged to grade I. The detailed information is concluded in Table 2 which was about all the cases of adverse events during the whole treatment cycles.

The results showed that the symptom of anemia was more obvious with the 20 mg/m^2 LBP level, and when the dosage level was set at 25 mg/m^2 as well as 30 mg/m^2, there was a relatively high incidence of leukopenia, neutropenia and anemia symptoms. It was indicated that the incidence of adverse reactions was proportional to the dose administered level. Besides, we found that the highest toxicities could be seen at a dose of 25 mg/m^2, the middle strength dosage. It might because that when the dose level was increased from 20 to 25 mg/m^2, the drug began to accumulate in the elderly causing an increased incidence of side effects, but when the dosage was raised to 30 mg/m^2, the corresponding Ccr of this group was 80 mL/min. Although the total dosage was increased, the drug metabolism becomes faster due to the larger Ccr, so that the drug does not accumulate easily in vivo, and the number of adverse reactions was less than that of the group with a dose of 25 mg/m^2.

Treatment results

Among 13 patients, the treatment cycle was ranged from 1 to 9 cycles with the average value of 3.54 ± 2.53 cycles, and similarly the dose range of LBP was 20–30 mg with the average value of 24.85 ± 3.96 mg. The cancer response was not evaluable in three patients because of the economic

Table 2 The cases of adverse events during the total treatment cycles

Adverse event	Total cases, *n* (%)	20 mg/m² LBP				25 mg/m² LBP				30 mg/m² LBP			
		I	II	III	IV	I	II	III	IV	I	II	III	IV
Hematological toxicities													
Leukopenia	19 (21.3)	1 (1.1)	0	0	0	8 (9.0)	3 (3.4)	2 (2.2)	0	3 (3.4)	1 (1.1)	1 (1.1)	0
Neutropenia	20 (22.5)	1 (1.1)	0	0	0	8 (9.0)	1 (1.1)	3 (3.4)	2 (2.2)	2 (2.2)	0	2 (2.2)	1 (1.1)
Thrombocytopenia	7 (7.9)	0	0	0	0	2 (2.2)	1 (1.1)	0	0	2 (2.2)	0	1 (1.1)	1 (1.1)
Anemia	30 (33.7)	4 (4.5)	2 (2.2)	0	0	8 (9.0)	6 (6.7)	5 (5.6)	0	1 (1.1)	2 (2.2)	2 (2.2)	0
Non-hematological toxicities													
Fever	1 (1.1)	0	0	0	0	1 (1.1)	0	0	0	0	0	0	0
Nausea	3 (3.4)	0	0	0	0	1 (1.1)	0	0	0	2 (2.2)	0	0	0
Anorexia	3 (3.4)	0	0	0	0	0	0	0	0	3 (3.4)	0	0	0
Skin pruritus	1 (1.1)	0	0	0	0	0	0	0	0	1 (1.1)	0	0	0
Hypoglycemia	1 (1.1)	1 (1.1)	0	0	0	0	0	0	0	0	0	0	0
Hypocalcemia	1 (1.1)	1 (1.1)	0	0	0	0	0	0	0	0	0	0	0
Hyponatremia	1 (1.1)	1 (1.1)	0	0	0	0	0	0	0	0	0	0	0
ALT elevation	1 (1.1)	1 (1.1)	0	0	0	0	0	0	0	0	0	0	0
AST elevation	1 (1.1)	1 (1.1)	0	0	0	0	0	0	0	0	0	0	0

[a]WHO criteria: leukopenia grade I, 3.0–3.9 × 10^9/L; leukopenia grade II, 2.0–2.9 × 10^9/L; leukopenia grade III, 1.0–1.9 × 10^9/L; leukopenia grade IV, 1.0 × 10^9/L; neutropenia grade I, 1.5–1.9 × 10^9/L; neutropenia grade II, 1.0–1.4 × 10^9/L; neutropenia grade III, 0.5–0.9 × 10^9/L; neutropenia grade IV, 0.5 × 10^9/L; thrombocytopenia grade I, 75.0–99.9 × 10^9/L; thrombocytopenia grade II, 50.0–74.9 × 10^9/L; thrombocytopenia grade III, 25.0–49.9 × 10^9/L; thrombocytopenia grade IV, 25.0 × 10^9/L; anemia grade I, Hb 5.9–6.7 mmol/L; anemia grade II, Hb 5.0–5.8 mmol/L; anemia grade III, Hb 4.0–4.9 mmol/L; anemia grade IV, Hb, 4.0 mmol/L

reasons or the diversion of other treatment protocol resulting in an early termination of this treatment regimen.

The median PFS and OS of all the enrolled subjects were 129 and 213 days, respectively (Fig. 2). The median PFS of patients for 30 mg/m² level was longer than that in "patients" with 20 and 25 mg/m² levels (373 vs. 129 days and 373 vs. 50 days). Similarly, the median OS of patients for 30 mg/m² level was also different between the other two levels (373 vs. 213 days and 373 vs. 113 days). A preliminary conclusion could be obtained that the higher the dose level administered, the better the therapeutic effect was obtained. Nevertheless, it was not a definitive conclusion because of the small sample size of this test, requiring a further research with large samples to confirm. The information of response and survival days is summarized in Table 3. Of the ten evaluable patients, stable disease was observed in six patients (60%), two patients (20%) experienced partial response and two patients (20%) were progressive disease within the total treatment. After the treatment of EL regimen, 38.5% patients obviously extended their survival time and the disease control rate could rise up to 80%. It was indicated that EL scheme could inhibit the SCLC disease procession and be more suitable for the treatment of SCLC male patients over 65 via the preliminary assessment.

Pharmacokinetic study

13 subjects who received EL regimen were included in the PK analysis population. PK parameters including terminal half-life ($t_{1/2}$), area under the curve ($AUC_{0–24}$, AUC

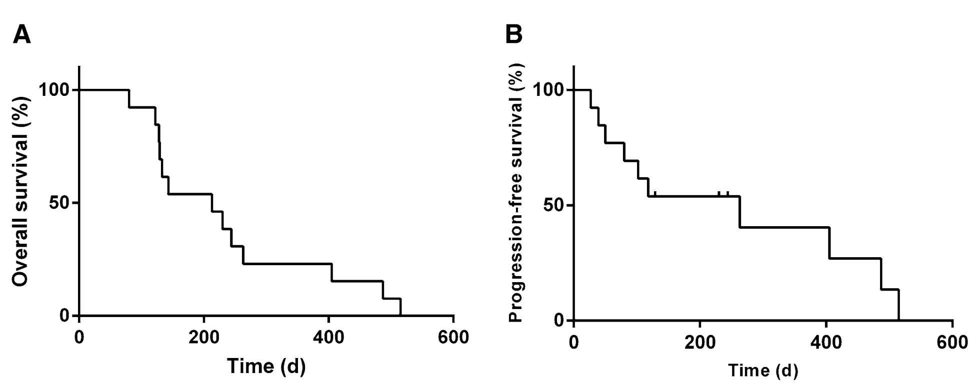

Fig. 2 Overall survival and progression-free survival of the subjects treated with three levels of EL treatment scheme (*n* = 13)

$_{0-\infty}$), maximum plasma concentration (C_{max}) and the time of C_{max} (T_{max}) are presented in Tables 4 and 5. The AUC_{0-24} values of LP-D1, LP-D2 were 1541.8 vs. 1609.2 ng h/mL ($P=0.31$) for 20 mg/m^2 level, 1765.9 vs.1761.4 ng h/mL ($P=0.04$) for 25 mg/m^2 level, and 2590.8 vs 2661.5 ng h/mL ($P=0.08$) for 30 mg/m^2. For the combined LBP, the value of AUC also showed an enhanced tendency and did not vary markedly with multiple dosages (4100, 4028 and 4084 ng h/mL, respectively). Mean half-life ranged from approximately 1.3–4.0 h across three levels. The average plasma concentration–time profiles for PK study comparing three dosages levels are displayed in Fig. 3.

Discussion

For most patients who suffered the same disease, although using the same treatment method as well as the same anti-tumor drug, given at unequal dosage will cause a huge difference in the aspects of efficacy and toxicity. Sometimes it was fatal. Therefore, assessing an appropriate dosage level for individualized chemotherapy has become a reasonable choice to improve the targeted treatment, reduce ineffective treatment and maximize the survival of patients. Among the current published articles, drug administration was mostly based on the body surface area (BSA) [19, 20] or weight [21], a normal and traditional mode. However, it exist a huge individual difference which could affect the efficacy and toxicity. For example, LBP is a drug metabolized by kidney, if the glomerular filtration rate (GFR) was ignored, patient who was administrated according to BSA only but with a low GFR could lead to a severe myelosuppression and thrombocytopenia. Thus, it is necessary to explore a newly individualized drug administration.

In clinical treatment, Ccr is usually used to evaluate renal function. It is because that most of the creatinine in the human body is filtered from the glomerulus, not reabsorbed by the renal tubules, and a small amount was excreted. Additionally, renal dysfunction is a major feature of the elderly reflecting the state of the body. Previous pharmacokinetic study [25] has confirmed that LBP has a good correlation between glomerular filtration rate (GFR) and creatinine clearance rate with a correlation coefficient of 0.91. Thus, we grouped patients into individualized treatments according to different Ccr levels. Patients with low Ccr are given low level dosage and vice versa. This

Table 3 Treatment results of responses and survival days to the EL scheme

Response (%)		Survival (days)		
Progressive disease (PD)	20	Progress-free survival (PFS)	AVE	207
Partial response (PR)	20		MED	129
Objective response rate (ORR)	20	Overall survival (OS)	AVE	238
Disease control rate (DCR)	80		MED	213

Table 4 The pharmacokinetics parameters of LP-D1 and LP-D2 in elderly plasma with three different dosage levels

Parameters	20 mg/m^2 ($n=5$)		25 mg/m^2 ($n=5$)		30 mg/m^2 ($n=3$)	
	LP-D1	LP-D2	LP-D1	LP-D2	LP-D1	LP-D2
C_{max} (ng/mL)	632.2 ± 461.6	632.2 ± 486.7	652.0 ± 480.5	686.0 ± 499.5	969.8 ± 523.5	1030.4 ± 612.2
$t_{1/2}$ (h)	6.9 ± 5.9	5.7 ± 3.5	3.5 ± 2.5	3.5 ± 2.6	2.0 ± 1.5	1.8 ± 1.3
T_{max} (h)	–	–	–	–	0.2 ± 0.3	0.2 ± 0.3
AUC_{0-24} (ng h/mL)	1541.8 ± 1038.5	1609.2 ± 1077.0	1765.9 ± 1165.9	1761.4 ± 1219.0	2590.8 ± 1335.5	2661.5 ± 1390.9
$AUC_{0-\infty}$ (ng h/mL)	1747.0 ± 1145.4	1824.1 ± 1222.4	2238.9 ± 1265.8	2314.1 ± 1335.9	2696.8 ± 1432.7	2756.3 ± 1475.5

Table 5 The pharmacokinetics parameters of combined LBP and element of Pt in elderly plasma with three different dosage levels

Parameters	20 mg/m^2 ($n=5$)		25 mg/m^2 ($n=5$)		30 mg/m^2 ($n=3$)	
	LBP	Pt	LBP	Pt	LBP	Pt
C_{max} (ng/mL)	2709.0 ± 2414.8	647.2 ± 174.6	2281.9 ± 1753.2	641.2 ± 296.6	2896.7 ± 868.7	610.0 ± 298.8
$t_{1/2}$ (h)	4.0 ± 5.0	16.0 ± 9.0	1.7 ± 0.3	19.1 ± 14.4	1.3 ± 1.0	5.9 ± 5.5
T_{max} (h)	–	–	–	–	–	0.1 ± 0.1
AUC_{0-24} (ng h/mL)	4099.9 ± 3966.0	4141.0 ± 1767.8	4027.9 ± 3011.1	3759.1 ± 1312.9	4084.0 ± 2232.6	2342.6 ± 1162.7
$AUC_{0-\infty}$ (ng h/mL)	4903.5 ± 4057.9	6832.8 ± 4077.9	14,984.4 ± 21,683.7	6221.8 ± 3186.3	4331.4 ± 2607.8	2899.0 ± 1640.4

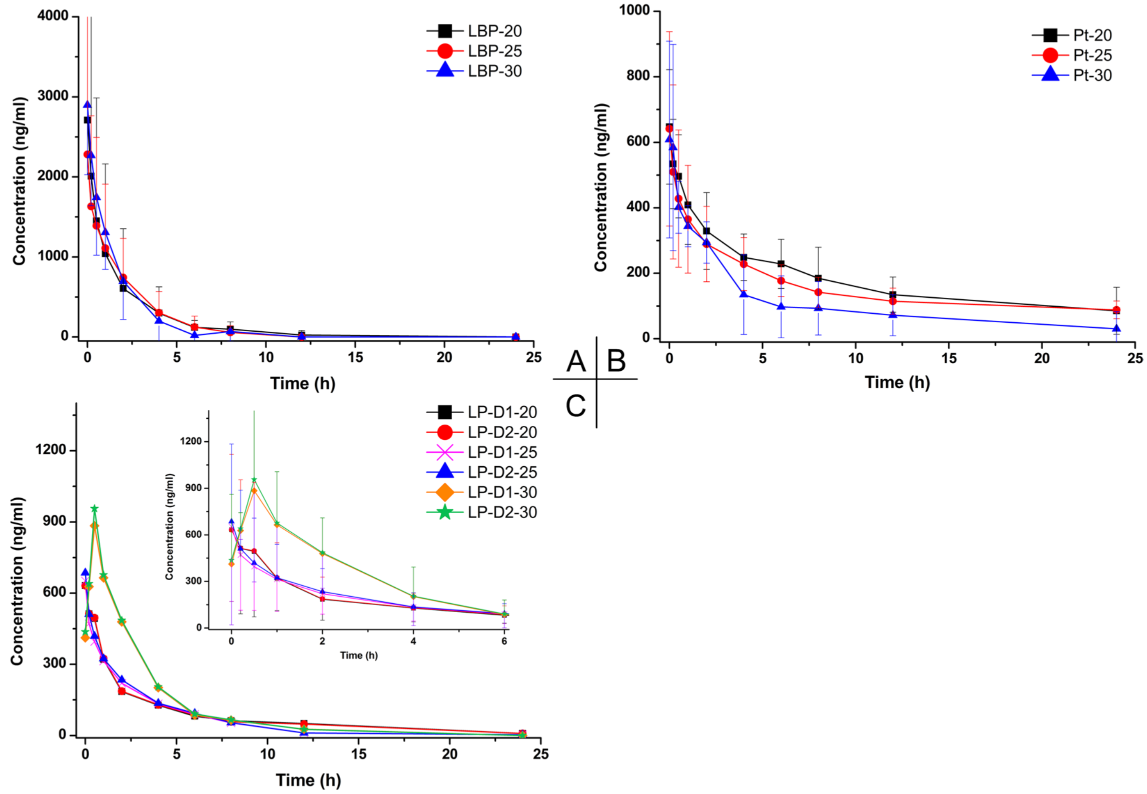

Fig. 3 The average concentration–time curves of **a** LBP; **b** platinum element and C).LP-D1 and LP-D2 in elderly subjects with SCLC

individualized group administration can reduce toxicity, improve compliance, and achieve safe treatment for the elderly.

For the treatment results, 13 subjects entered this trail were closely observed and recorded the adverse events during the whole process. Compared with the similar study [26] treating the SCLC elderly with amrubicin (AMR), the percent of SD was raised from 48 to 60%, and PD to PR is similar to that in the literature. While the OS and PFS were higher than our study, it was probably because the small size of evaluable patients. It was worth noting that for the common adverse events, the incidence probability of Grade 3 or 4 neutropenia and leukopenia was dropped by nearly half from 58 to 31% and 42 to 23%, respectively. In the comparison of another literature [27], the ratio of Grade 3 or 4 neutropenia and leukopenia was also decreased from 58 to 31% and 56 to 23%, respectively. Besides, it can be seen from our treatment results of PFS and OS that the survival cycle of 38.5% patients were prolonged and the rate of disease control was up to 80%. It was indicated that our individualized EL regimen could reduce the incidence of adverse reactions, improve the safety and the compliance of therapeutic drugs, especially for the elderly population. However, due to the small number of subjects, this result requires further clinical study to confirm.

Results of the PK analysis revealed that PK profiles of LP-D1 and LP-D2 were similar at the same administration dosage (AD) level and the detected concentration of two diastereoisomers increased gradually with increasing dose, which were consistent with the literature report [25]. The results indicated that different molecular configuration of LBP had no influence on the PK behaviors. In addition, across the 20, 25, 30 mg/m^2 three dose groups, AUC and C_{max} increased in a dose-independent manner over the evaluated dosage range of 20–30 mg. However, $t_{1/2}$ value decreased as the dose increasing, which was attributed to the elevated Ccr causing a faster drug metabolism rate [24]. Comparing with the existing study [25], the half-life of intact LBP was similar to the level of LBP 25 mg/m^2 (2.2 h vs. 1.7 h). What' more, in our study design, the purpose of grouping 13 patients according to Ccr was to ensure the safety of administration for the elderly. PK results about the change of AUC_{0-24} value, which could reflect toxicity indirectly, indicated that the drug retention concentration in vivo was approximate in different groups within 24 h and no drug accumulation was observed across the increased dosages.

Additionally, we also investigated the relationship between the clearance of intact lobaplatin and creatinine clearance and calculated the CLz of intact lobaplatin for each patient as follows: 0.003, 0.002, 0.009, 0.004, 0.010, 0.006, 0.006, 0.006, 0.012, 0.003, 0.004, 0.005 and 0.006 L/h/m^2. For the level of 20 mg/m^2 LBP, the average value of CLz was 3.8×10^{-3} L/h/m^2, for 25 mg/m^2 LBP, the mean value was 5.4×10^{-3} L/h/m^2 and similarly, the 8.5×10^{-3} L/h/m^2 for 30 mg/m^2 LBP. A linear regression equation was done with Ccr and CLz of 13 people ($y=0.1822x-6.0875$, $r=0.73$), we found that there was a correlation between intact lobaplatin clearance and creatinine clearance. Compared with the reference reported before [25], the value of r was lower (0.73 vs. 0.91). It was probably because the sample size in our study was small, and it was indeed a defect in the initial clinical evaluation. However, the positive correlation between CLz and Ccr could be still observable, which was consistent with the existing report.

It can be concluded that this phase II study was first examined the pharmacokinetic behavior of different LBP forms at different dosage levels in SCLC elderly patients. Additionally, this individual administrated strategy, LBP (20, 25, 30 mg/m^2) in combination with VP-16 (100 mg/m^2), could inhibit the disease process, reduce the incidence of adverse reactions and improve the safety of treatment via the preliminary assessment for the elderly male patients with extensive-stage SCLC. However, there were still several limitations to this study. Firstly, lacking the female composition among the enrolled subjects was a disadvantage causing the subject unrepresentative and a certain impact on the results. Secondly, the number of subjects in this clinical trial is small, and it will cause a large deviation to the final result. The result requires further clinical study to confirm and then draw the scientific conclusion. Although there were some limitations in our study, the results could still provide guidance to a certain extent for further investigation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional. Informed consent was obtained from all individual participants included in the studies.

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