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The effectiveness and safety of lienal polypeptide combined with chemotherapy or chemoradiotherapy for non-small cell lung cancer patients in real world

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Abstract

Chemotherapy/chemoradiotherapy are still the fundamental treatment for advanced lung cancers. To reduce side effects and improve life quality, lienal polypeptide (LP) could be used in combine with chemotherapy/chemoradiotherapy. Moreover, LP could regulate immune system and possibly reduce the side effects of chemotherapy drugs.

In our study, 1658 lung cancer patients from 10 hospitals were retrospectively analyzed and divided into LP group and non-LP group by whether using LP during their treatment. Kaplan-Meier curves and Log-rank test was used to detect the difference of progression-free survival and overall-survival between the 2 groups. Two-sided *P*-values of less than .05 indicated statistical significance. All analyses were performed with SAS software (version 9.4 SAS Institute, Cary, NC).

Results showed that the number of patients who had progressed diseases in LP group and control group were 532 (64.2%) and 507 (61.2%). Log Rank test showed that median progression-free survival for LP group was 12.1 months and 11.4 months for control group ($P = .3478$). Statistical analyses revealed significantly difference in overall-survival between LP group and control group (23.6 months vs 18.9 months, $P = .0177$). The overall adverse effect rates were non-significantly different with 9.9% in the LP group and 9.3% in the non-LP group ($P = .6767$).

In conclusion, our research results indicated that LP used in combination with chemotherapy/chemoradiotherapy was a safe and effective treatment for patients of advanced lung cancer. LP could also reduce the adverse effects of chemotherapy/chemoradiotherapy, thereby improving patients' life qualities, and potentially improving prognosis.

Abbreviations: CRT = chemoradiotherapy, CT = chemotherapy, LP = lienal polypeptide, NK cells = natural killer cells, NSCLC = non-small cell lung cancer, OS = overall-survival, PD-1 = programmed cell death protein 1, PD-L1 = programmed death-ligand 1, PFS = progression-free survival.

Keywords: active, adjuvant, chemotherapy, immunity, lung neoplasms

1. Introduction

Lung cancer has the second most morbidity among malignancies in the world but kills most patients than any other malignancies.[1] A large proportion of lung cancer patients were diagnosed at late stage and lost the opportunity of radical lobectomy. In the United States, 79% of newly diagnosed lung cancer patients had their regional lymph node or further organ metastasized. Chemotherapy (CT) and/or radiotherapy have been the standard treatment for those patients for decades. In recent years targeted-therapy and immunotherapy drew much attention as they significantly prolonged the overall-survival (OS) and progression-free survival (PFS) for advanced-stage non-small cell lung cancer (NSCLC) patients. However, most patients receive targeted-therapy and immunotherapy must be driven gene positive or have high programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) expression, who accounts for only a small proportion of lung cancer patients. Moreover, immunotherapy is normally used in combined with CT rather than alone to get best prognosis. Thus, CT and/or radiotherapy remains the basic treatment for advanced-stage lung cancer.

Inevitably, side effects often come with CT and/or radiotherapy, such as nausea, myelosuppression, and hypo-immunity. This may lead to severe secondary infection and sometimes, even life threatening. As a result, complementary medicine is often used to reduce side effects and improve immune statues.

Lienal polypeptide (LP) is a kind of spleen extraction from healthy calf. Lienal polypeptide may possibly regulate immune system by correcting the disorder and enhance the non-specificity immune system. When used together with CT regimens, lienal polypeptide could probably reduce the side-effects and improve life quality of patients.

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The authors report no conflicts of interest.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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LP injection has been widely used in the treatment of multiple malignancy tumors. Investigations on the combination of LP injection and CT in breast cancer, colorectal cancer, lung cancer, esophageal cancer, pharyngeal cancer, urethral cancer, and non-Hodgkin lymphoma showed safety and low adverse effects.[2,3] We; therefore, hypothesis that lung cancer patients could also benefit from LP injection with CT regimens during and after their treatment. In this retrospective, multicenter study, the effectiveness, and safety of LP combined with CT and chemoradiotherapy (CRT) were analyzed, focusing on the progression-free survival and overall survival, as well as the characteristics of patients and eliminating the CT adverse effects in real world.

2. Materials and methods

2.1. Patients

A multicenter, retrospective study was conducted in 10 hospitals, recruiting 2357 NSCLC patients with inclusion and exclusion criteria as following:

Inclusion criteria:

(1) intact clinical data,
(2) pathologically confirmed stage IIIB/IV NSCLC,
(3) received platinum-based doublet CT or CRT

Exclusion criteria:

(1) cancer history other than NSCLC,
(2) patients who received targeted therapy
(3) usage of immune regulator other than LP (thymopeptides, thymopentin, thymopeptides-α1, calf spleen extractive injection, placenta polypeptide, lentinan, Shen Qi Fu Zheng).
(4) received immunotherapy or with basic disease of immune system.

After data reviewing, 2357 patients accorded with the inclusion criteria, including 829 patients who received combined treatment of LP and CT/CRT and 1528 patients who received CT or CRT only. Propensity score match was performed with variants of age, sex, TNM stage, metastasis site, CT regime, and treatment cycles. The 2 groups were matched at 1:1 ratio to reach the best statistical efficacy. Finally, 1658 patients were selected including 829 patients receiving LP treatment in the study group and 829 matched patients receiving non-LP treatment in the control group. This study was approved by the Ethic Committee of Fourth Hospital, Hebei Medical University.

2.2. Statistical analysis

Nearest available neighbor without replacement method (greedy matching algorithm), 1 method of propensity scores matching method, was used to match the control group to the treatment group on a 1-to-1 ratio based on a set of covariates, including age, gender, tumor stage, metastasis sites, platinum-based doublet CT and cycles.

Categorical variables (such as diseases progressed status, overall survival status, and adverse effects) are reported as counts and percentages, and Chi-squared tests or Fisher exact tests were used to test for differences between groups. For PFS and OS, the Kaplan–Meier curves was plotted by treatment allocation and Log-rank test was used to detect the difference between 2 curves; median PFS and OS and its 95% confidence interval, 1, 2, and 3-year rate was computed. Two-sided *P* values of less than .05 indicated statistical significance. All analyses were performed with SAS software (version 9.4 SAS Institute, Cary, NC).

3. Results

3.1. Patients characteristics

In this study, there were 1191 male and 467 female patients, with age from 24 to 84 years (median age: 58.1 years). Table 1 showed the details of patients' clinicopathological characteristics.

Disease characters were analyzed and matched. The study only recruited advanced stage cancer patients. IIIB and IV stage patients were 135 and 694 in LP group, while 145 and 684 in non-LP group. Moreover, the pathology types were 179 squamous cell carcinomas in LP group, and 203 in non-LP group. The other pathology types of cancers were adenocarcinoma, adeno-squamous carcinoma, and large cell carcinoma, accounting for 389, 20, and 2 cases in LP group, meanwhile 389, 14, and 4 cases in the non-LP group.

3.2. PFS and median PFS

During the 5 years study, number of patients who had their diseases progressed in the LP group and control group were 532 (64.2%) and 507 (61.2%). Progression in the LP group is slightly higher than control group (Table 2).

Log Rank test was conducted in both groups and survival curves were generated. Median PFS for LP group was 12.1 months and 11.4 months for control group ($P = .3478$). There was no significant difference between LP group and control group in PFS (Fig. 1). However, 1, 2, and 3-year PFS in LP group were better than the control group (50.39% vs 47.71%, 24.64% vs 23.42%, 15.65% vs 11.84%) (Table 3).

3.3. OS and median OS

Deaths happened in the 2 groups were 366 (44.1%) in the LP group and 362 (43.7%) in control group (Table 4). Statistical analyses revealed significantly difference in OS between LP group and control group (23.6 months vs 18.9 months $P = .0177$) (Fig. 2). Moreover, the 1, 2, and 3-year OS were higher in the LP than in the control group (71.56% vs 66.72%, 48.94% vs 42.24%, 34.17% vs 25.62%) (Table 5).

3.4. Adverse effects

The radiotherapy/CRT -related adverse effects among all the 1658 patients were calculated and analyzed statistically. The overall adverse effect rates were non-significantly different with 9.9% in the LP group and 9.3% in the non-LP group ($P = .6767$). However, the control group experienced more erythrocytopenia, leukocytosis, thrombocytosis, elevated glutamyl transpeptidase, elevated urea nitrogen, and abnormal heart function, while non-LP group had more digestive reacts including nausea. The rates of those adverse effects were shown in Table 6.

4. Discussion

The incidence of lung cancer has increased significantly during the last several decades. As is reported by the National Cancer Center of China in 2015, it is estimated that there were 733.3 thousand newly diagnosis lung cancer patients and sadly 610.2 thousand patients died of lung cancer in 1 year.[4] Further on, the

Table 1

Baseline of patients' clinicopathological characteristics.

Baseline	LP group (N = 829)	Non-LP group (N = 829)	Total	*P* value
Sex				.9565
Male	595 (71.8%)	596 (71.9%)	1191 (71.8%)	
Female	234 (28.2%)	233 (28.1%)	467 (28.2%)	
Age				.6992*
Cases	829	829	1658	
Mean (SD)	58.0 (9.28)	58.2 (9.40)	58.1 (9.34)	
BMI, kg/m^2				.0617*
Cases (missed cases)	636 (193)	647 (182)	1283 (375)	
mean (SD)	22.9 (3.09)	23.3 (3.39)	23.1 (3.25)	
ECOG group				.0247
0	9 (4.7%)	10 (10.1%)	19 (6.5%)	
1	136 (70.8%)	74 (74.7%)	210 (72.2%)	
2	33 (17.2%)	6 (6.1%)	39 (13.4%)	
≥3	14 (7.3%)	9 (9.1%)	23 (7.9%)	
Missed cases	637	730	1367	
KPS group				.1101
<80	12 (17.9%)	17 (10.4%)	29 (12.6%)	
(80, 90)	35 (52.2%)	108 (66.3%)	143 (62.2%)	
≥90	20 (29.9%)	38 (23.3%)	58 (25.2%)	
Missed cased	762	666	1428	
Primary focal				
Right lung (lobe not specified)	34 (4.1%)	54 (6.5%)	88 (5.3%)	
Right upper lobe	93 (11.2%)	78 (9.4%)	171 (10.3%)	
Right lower lobe	66 (8.0%)	77 (9.3%)	143 (8.6%)	
Right middle and lower lobe	4 (0.5%)	4 (0.5%)	8 (0.5%)	
Right middle lobe	34 (4.1%)	47 (5.7%)	81 (4.9%)	
Right bronchus	35 (4.2%)	14 (1.7%)	49 (3.0%)	
Left lung (lobe not specified)	35 (4.2%)	53 (6.4%)	88 (5.3%)	
Left upper lobe	87 (10.5%)	99 (11.9%)	186 (11.2%)	
Left lower lobe	89 (10.7%)	92 (11.1%)	181 (10.9%)	
Left bronchus	32 (3.9%)	13 (1.6%)	45 (2.7%)	
Others	11 (1.3%)	10 (1.2%)	21 (1.3%)	
Missed	309 (37.3%)	288 (34.7%)	597 (36.0%)	
TNM				.5121
IIIB	135 (16.3%)	145 (17.5%)	280 (16.9%)	
IV	694 (83.7%)	684 (82.5%)	1378 (83.1%)	
Metastasis	465 (56.1%)	515 (62.1%)	980 (59.1%)	.0125
Brain	83 (10.0%)	74 (8.9%)	157 (9.5%)	.4503
Bone	163 (19.7%)	176 (21.2%)	339 (20.4%)	.4286
Liver	56 (6.8%)	56 (6.8%)	112 (6.8%)	1.0000
Renal and adrenal	45 (5.4%)	49 (5.9%)	94 (5.7%)	.6710
Ipsilateral lung	133 (16.0%)	134 (16.2%)	267 (16.1%)	.9467
Pleura	71 (8.6%)	67 (8.1%)	138 (8.3%)	.7221
Other side	100 (12.1%)	114 (13.8%)	214 (12.9%)	.3051
Pathology type				.4072
squamous cell carcinoma	179 (30.3%)	203 (33.3%)	382 (31.8%)	
Adeno-carcinoma	389 (65.9%)	389 (63.8%)	778 (64.8%)	
Adeno-squamous carcinoma	20 (3.4%)	14 (2.3%)	34 (2.8%)	
Large cell carcinoma	2 (0.3%)	4 (0.7%)	6 (0.5%)	
Missed cases	239	219	458	
Differentiation				.4837
Low grade	34 (42.5%)	62 (51.2%)	96 (47.8%)	
Moderate grade	26 (32.5%)	26 (21.5%)	52 (25.9%)	
Low to moderate grade	13 (16.3%)	21 (17.4%)	34 (16.9%)	
High grade	4 (5.0%)	4 (3.3%)	8 (4.0%)	
Moderate to high grade	3 (3.8%)	7 (5.8%)	10 (5.0%)	
Un-differentiated	0 (0.0%)	1 (0.8%)	1 (0.5%)	
Missed cases	749	708	1458	
Radiotherapy history	181 (21.8%)	117 (14.1%)	298 (18.0%)	<.0001

BMI = body mass index, ECOG = Eastern Cooperative Oncology Group, KPS = Karnofsky performance scale.

* *P*-values with marked are from *t* test. Other *P* values are from Chi-square test.

Table 2

Progression in LP group and control group.

	Progression		Nonprogression		Total
Non-LP	507	61.2%	322	38.8%	829
LP	532	64.2%	297	35.8%	829
total	1039	62.7%	619	37.3%	1658

LP = lineal polypeptide.

5-year survival rates of lung cancer were also frustrating, with merely around 50% for even local lesion.[5] Targeted-therapy and immunotherapy attracted much attention in the treatment of lung cancer, but most patients still largely rely on CT due to lack of driving gene or high PD-1/PD-L1 expression.

The spleen is an important lymphoid organ maturing lymphocytes. Immune function could be indicated by the ratio of CD3+CD4+/CD3+CD8+ cells.[6] Spleen cells, extracted from thymopentin treated mice, could inhibit tumor growth in vitro without cytotoxic drugs. This experiment was carried out by Lau and his colleagues showing the immune enhancement of spleen cells.[9]

LP is an immune regulator extracted from spleen tissues, exerting several influences on the immune system. It has been reported to be able to regulate immune response and inhibit tumor growth by several studies.[10,11] LP helps keep immune system functioning well by improving non-specific immune function and accelerating T cell maturation.[12] Moreover, bone marrow cells could also be stimulated to produce more hemocytes so that immune response could be enhanced, and erythrocytes were increased.[13] Another mechanism that LP enhances immune system is activating natural killer cells (NK cells). To reveal this mechanism, an in vitro experiment was carried out and showed that LP solution activated NK cell through androgen receptor and major histocompatibility complex class I polypeptide-related sequence A/B pathway.[14] In vitro experiments also showed that LP worked well together with cyclophosphamide and significantly reduced the tumor sizes of Lewis lung carcinoma-bearing mice. Furthermore, LP was also found to improve the immune system through phagocytosis-related pathway. LP treated mice were found to have lower phagocytosis-related proteins. These findings indicated that LP was a potential anti-immunosuppression substance, which was induced by CT.[6] Jing Wang et al. carried in vitro and in vivo studies investigating the dual regulatory function of lienal peptide. Their research showed that lienal peptide could both decrease pro-inflammatory cytokines through NF-κB pathway while increase the immunologic function of immunosuppressed mice by enhance the bone marrow B lymphocytes, spleen lymphocytes, NK cells, and peritoneal macrophages.[7] Besides immunologic function enhancement, another study on the crude extract from Middle Asian tortoise *Testudo horsfieldii* spleen revealed that a peptide of the extract derivative could protect the mice from lethal doses of radiation by up-regulating the hemopoietic system.[8]

Studies have demonstrated that combined chemoimmunotherapy had the ability to reduce tumor size, inhibiting metastasis, and increasing CD4+ lymphocytes while reducing CD8+ lymphocytes.[15] In a randomly controlled trial, LP combined with FOLFOX CT regimen obtained relatively good wellbeing and strengthened the immune system in colon cancer patients. A total of 84 patients were recruited in the study, 42 in control and 42 in observation group. CT alone and CT combined with LP

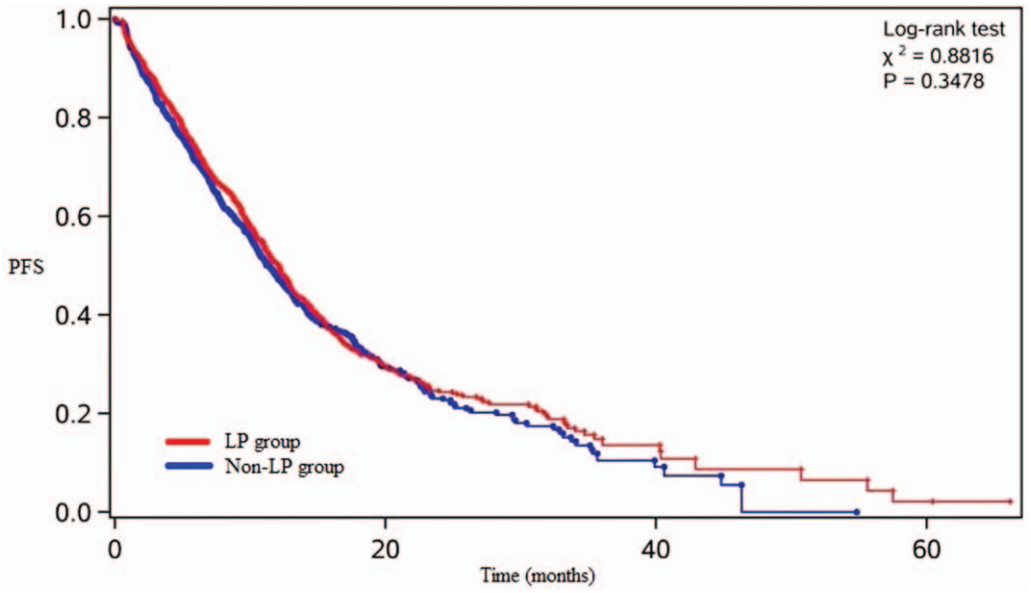

Figure 1. Log-rank test curve for the progression-free survival (PFS) of LP group and non-LP group. The *x*-axes indicated PFS time (months) and *y*-axes indicated the percentage of PFS patients among all patients. Results showed that LP could not prolong the PFS of the patients in the LP group ($P = .3478$). LP = lienal polypeptide.

Table 3

PFS and median PFS in LP group and control group.

	1-yr PFS	2-yr PFS	3-yr PFS	Median PFS (mo) (95% CT)	LogRank test	*P*-value
Non-LP	47.71%	23.42%	11.84%	11.4 (10.4, 12.4)	0.8816	.3478
LP	50.39%	24.64%	15.65%	12.1 (11.1, 12.9)		

LP = lineal polypeptide, PFS = progression-free survival.

Table 4

Survival status in LP group and control group.

	Survival status				
	Surviving		Death		
	n	%	n	%	Total
Non-LP	467	56.3	362	43.7	829
LP	463	55.9	366	44.1	829
Total	930	56.1	728	43.9	1658

LP = lineal polypeptide.

injection were administered in the 2 groups. Combined therapy group showed significantly higher Karnofsky performance scale scores of 85.9 ± 6.5 than 74.3 ± 5.9 in control group, CD4+T/CD8+T cells ratio and number of NK cell.[12] In another research, Huang and his colleagues studied the combination of LP injection and CT, found that the incidences of adverse effects were relatively low among these cancer patients and no treatment related death happened. LP combined with CT was a safe treatment for cancer patients.[2] These encouraging results inspired researchers to conduct further studies on the combined chemoimmunotherapy.

In our study, we retrospectively analyzed 1658 lung cancer patients. The patients all received CT/CRT, and subsequently were divided into 2 groups by whether used LP as part of adjuvant therapy. Results showed significantly better median overall survival for CT/CRT combined with LP group. The improvement of overall survival is closely related to the well-functioning of the patients' immune system. Additionally, the rate of erythropoiesis is significantly decreased in LP treatment group. This finding is in accordance with that LP could help the recovery of bone marrow function to produce enough erythrocytes.

From the results, LP also exhibited considerable good impact on the median PFS and eliminating adverse effect of CT and/or radiotherapy. As LP is rather an immune system regulator than activator, we cannot place too many expectations on LP like PD-1/PD-L1 antibodies. For this reason, it is not surprising that not much statistically significant improvements were seen in the LP group. However, we still observed quite good improvements in LP group. Moreover, researchers also demonstrated that LP group patients had significantly better Karnofsky performance scale scores and better life quality.

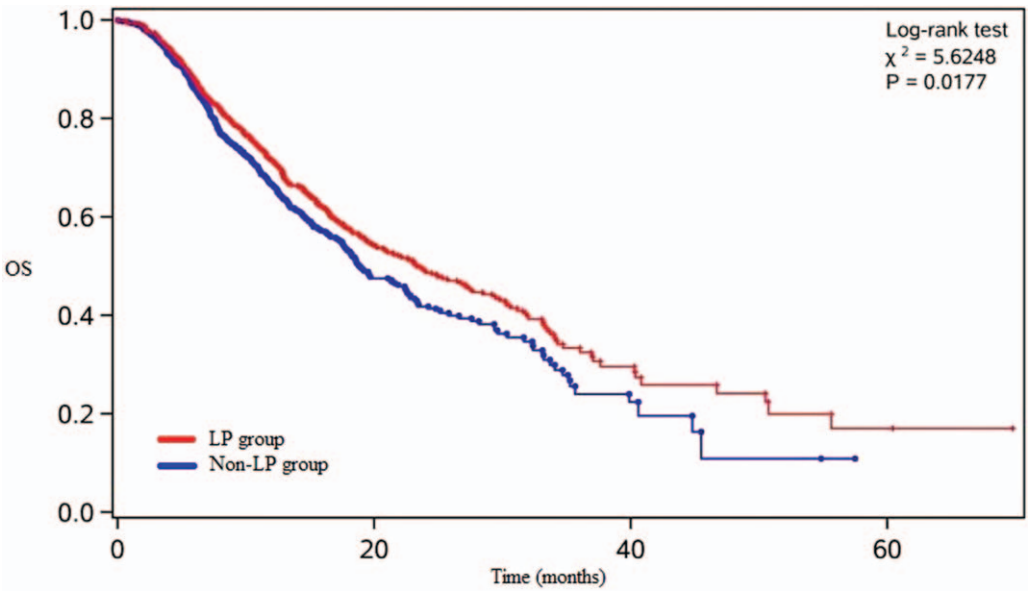

Figure 2. Log-rank test curve for the overall survival (OS) of LP group and non-LP group. The *x*-axes indicated OS time (months) and *y*-axes indicated the percentage of OS patients among all patients. Results showed significant difference between the 2 groups (*P* = .0177). LP = lienal polypeptide.

Table 5

OS and median OS in LP group and control group.

	1-yr OS	2-yr OS	3-yr OS	Median OS (mo) (95% CT)	LogRank test	*P* value
Non-LP	66.72%	42.24%	25.62%	18.9 (17.7, 22.4)	5.6248	.0177
LP	71.56%	48.94%	34.17%	23.6 (20.2, 27.4)		

LP = lineal polypeptide.

Table 6

Adverse effects in LP group and control group.

Adverse effects	LP group (N = 829)	Non-LP group (N = 829)	Total	*P* value
Overall	82 (9.9%)	77 (9.3%)	159 (9.6%)	.6767
Erythro-cytopenia	1 (0.1%)	14 (1.7%)	15 (0.9%)	.0007
Leukopenia	12 (1.4%)	11 (1.3%)	23 (1.4%)	.8337
Neutropenia	4 (0.5%)	5 (0.6%)	9 (0.5%)	1.0000*
Thrombo-cytopenia	5 (0.6%)	1 (0.1%)	6 (0.4%)	.2179*
Erythroblastia	0 (0.0%)	3 (0.4%)	3 (0.2%)	.2495*
Leukocytosis	2 (0.2%)	9 (1.1%)	11 (0.7%)	.0342
Neutrophilia	0 (0.0%)	7 (0.8%)	7 (0.4%)	.0154*
Thrombocytosis	1 (0.1%)	11 (1.3%)	12 (0.7%)	.0038
Anemia	12 (1.4%)	20 (2.4%)	32 (1.9%)	.1533
Nausea	16 (1.9%)	4 (0.5%)	20 (1.2%)	.0069
Diarrhea	1 (0.1%)	0 (0.0%)	1 (0.1%)	1.0000*
Weak	5 (0.6%)	6 (0.7%)	11 (0.7%)	.7623
Fever	2 (0.2%)	2 (0.2%)	4 (0.2%)	1.0000*
Dyspnea and cough	4 (0.5%)	6 (0.7%)	10 (0.6%)	.5258
Hypo-proteinemia	4 (0.5%)	11 (1.3%)	15 (0.9%)	.0694
Gastrointestinal reaction	4 (0.5%)	2 (0.2%)	6 (0.4%)	.6869*
Other digestive tract reacts	14 (1.7%)	1 (0.1%)	15 (0.9%)	.0007
Abnormal liver function	1 (0.1%)	3 (0.4%)	4 (0.2%)	.6245*
Elevated glutamyl Transpeptidase	1 (0.1%)	13 (1.6%)	14 (0.8%)	.0013
Elevated urea nitrogen	1 (0.1%)	11 (1.3%)	12 (0.7%)	.0038
Urea nitrogen reduction	5 (0.6%)	1 (0.1%)	6 (0.4%)	.2179*
Abnormal heart function	1 (0.1%)	11 (1.3%)	12 (0.7%)	.0038
Rash	7 (0.8%)	4 (0.5%)	11 (0.7%)	.3641

LP = lineal polypeptide.

* *P*-values with marked are from Fisher exact test. Other *P*-values are from Chi-square test.

We must admit that there seemed to be more adverse effect in the LP group in subgroup analysis, especially in patients older than 60. Elderly patients were weaker and probably could not tolerate more medications, which could possibly cause some adverse effect. Thus, we should prescribe medicines including LP for elderly patients more intriguingly in order to avoid as much adverse events as possible.

In conclusion, our research results indicated that LP used in combination with CT/CRT was a safe and effective treatment for patients of advanced stage lung cancer. LP could also reduce the adverse effects of CT/CRT, thereby improving patients' life qualities, and potentially improving prognosis. However, further investigations are still required to illustrate the specific mechanism to enhance the immunity of LP.

5. Conclusion

In conclusion, our research results indicated that LP used in combination with CT/CRT was a safe and effective treatment for patients of advanced stage lung cancer. LP could also relieve the painfulness of the adverse effects of CT/CRT, thereby improving patients' life qualities, and potentially improving prognosis.

Author contributions

Conceptualization: Junfeng Liu.
Data curation: Zhe Wang.
Formal analysis: Zhe Wang.
Project administration: Junfeng Liu.
Software: Zhe Wang.
Supervision: Junfeng Liu.
Writing – original draft: Zhe Wang.
Writing – review & editing: Junfeng Liu.

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