Meta Analysis of Lentinan Injection plus Cisplatin in Treatment of Malignant Pleural Effusion

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Abstract: **Objective** To evaluate the efficacy and safety of lentinan injection plus cisplatin (LIC) in the treatment of malignant pleural effusion (MPE). **Methods** We searched the database of Cochrane Library, PubMed, EMBASE, ISI Web of Knowledge, Chinese Biomedical Literature Database, Chinese Scientific Journals Full-text Database, Chinese Journal Full-text, and Google Scholar, etc., up to February 28th, 2011 to identify randomized controlled trials (RCTs) about lentinan injection (LI) for MPE, evaluate the quality of the included studies, and analyze the data by Cochrane Collaboration's RevMan5.0 software. **Results** Twenty-nine RCTs involving 1831 patients were included. Meta analysis results suggested that there were some differences when comparing LIC with control groups suffering from MPE, for LIC could improve the near-term curative effect and the quality of life to some extent. Besides, compared with chemotherapy alone, LI plus chemotherapy had an advantage in relieving adverse reactions, such as gastrointestinal reactions, myelosuppression, chest pain, and general malaise. **Conclusion** The current evidence indicates that LI may have adjuvant therapeutic effects for MPE.

Key words: chemotheraphy; cisplatin; lentinan injection; malignant pleural effusion; meta analysis
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Introduction

Malignant pleural effusion (MPE), which is generated by lung cancer or other malignancies involving the pleura or primary pleural tumors, is a significant kind of common complication of advanced tumors (Yan, Qian, and Liu, 2009). It is generally acknowledged that the proportion occupied by MPE in the pleural effusion is 38%－53%, namely, 75% of MPE are caused by lung cancer and breast cancer, while 5%－10% could not pertain to any kind of primary tumor lesion (American Thoracic Society, 2000), which made much difficulty for the treatment. The existence of MPE constantly suggests that the tumor has spread and is also a sign of terminal diseases which could not be cured by any means of surgery (Zhang *et al*, 2009). Chemotherapy drug, which could be locally injected into pleural cavity, is a vital direction to effective treatments after closed drainage, owing to not only a local direct antitumor therapy but also chemical pleuritis caused by stimulation, even pleural adhesion and then pleural cavity occlusion. Commonly-used chemotherapy drugs are Cisplatin, Carboplatin, Bleomycin, and so on (Wu, 2000). Nevertheless, unitary chemotherapy drug more often than not leads to serious adverse reactions, so it severely reduces the patients' life quality, such as gastrointestinal reactions, hair loss, myelosuppression, liver or kidney toxicity, and all that. Nowadays, a great many of experts at home and abroad are all trying to hunt possible ways that chemotherapy drugs could combine with other drugs or auxiliary approaches for a treatment goal, involving high efficiency and low toxicity.

In recent years, biological therapy in the treatment of MPE has attracted more and more attention, which could enhance antitumor effect for the host also reduce the immunity inhibition resulted by tumor. Still, it also

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has some advantages such as significant improvement in symptoms, ameliorating quality of life, and prolonging survival time. Lentinan, one of biological response modifiers, which plays an important role in broad antitumor effect and has no cytotoxicity, is a kind of high purity dextran. If by intrapleural administration, lentinan could also activate immune system, inhibit and kill tumor cells, stimulate pleura to secrete much more fibrin, and then result in pleural adhesion and reduction of pleural effusion, finally achieve the purpose of effective control of pleural effusion (Zhao, 1993; Jin, 2009).

With extremely rapid advances in related medical fields, more and more reports about lentinan injection plus cisplatin (LIC) after closed drainage of pleural cavity in the treatment of MPE appeared vastly. However, many aspects such as clinical efficacy and toxicity could not agree with each other. Thus, they collected all the randomized controlled trials (RCTs) as many as they could and then used the Cochrane systematic review format in order to evaluate the efficacy and safety of lentinan objectively, looking forward to providing reliable evidence for clinicians.

Materials and methods

Literature search

We searched PubMed (1966 － Feb, 2011), EMBASE (1974－Feb, 2011), the Cochrane Library (issue 2, 2011), ISI Web of Knowledge (1966－Feb, 2011), Chinese Biomedical Literature Database (1978－Feb, 2011), Chinese Journal Full-text Database (1979－Feb, 2011), Chinese Science and Technology Periodicals Database (1989－Feb, 2011), and Google Scholar etc. The search strategy was "(lentinan OR lentinan injection) AND (cisplatin OR cisplatinum OR platinum OR *cis*-platinum OR neoplatin OR DDP) AND (malignant pleural effusion * OR MPE)". Two reviewers conducted the search independently, and then we also evaluated the quality of studies using Cochrane recommendations. If there existed any difference, they resolved issues through discussion with the third one.

Included trials

Types of studies All RCTs of LIC after closed drainage of pleural cavity in the treatment of MPE were included.

Types of participants The included patients are all adults (age > 18 years) with MPE, who were confirmed by pathology and/or cytology as advanced cancer patients. Sex, ethnicity, and nationality were not limited. Karnofsky Performance Status (KPS) scale of all patients was more than 40 or the survival time was more than two months. Patients from included trials have not received chemotherapy in recent one month, and without contraindication or problem with liver or kidney. Besides, they also have had formal haematology and electrocardiogram, and certainly without doubt, no serious internal medicine or infection diseases.

Types of outcome measures The primary effectiveness outcome was as follows: 1. near-term curative effect, such as complete remission (CR), partial remission (PR), and CR + PR; 2. increased rate of Karnofsky score; 3. diversification of Karnofsky score after treatment. Furthermore, there existed other adverse reaction indicators such as gastrointestinal reactions, fever, myelosuppression, chest pain, liver function damage, kidney function damage, hair loss, general malaise, and stomatitis, etc.

Document screening and data extraction

The review was undertaken by two reviewers. The search strategy described above was developed and performed to identify eligible studies. The results, combined with all titles, abstracts, or the full text when necessary, were screened independently by two authors. In cases of disagreement between the two authors, the full articles were obtained and inspected independently by a third author. Data extraction was carried out by the same reviewers independently using standard data extraction forms. It was developed to record the details of study design, participants, setting and timing, intervention, characteristics, and outcomes.

Quality evaluation

Two authors conducted the search independently and evaluated the quality of these included studies using simple method that is recommended by *Handbook of Cochrane Collaborate* (Higgins, 2008). The quality items assessed were sequence generation, allocation concealment, blinding of participants, incomplete outcome data, free of selective reporting, and other sources of bias. They recorded problems in respect of these issues in full, and for individual studies each criteria was assigned a label of "yes", "unclear", or "no" to estimate risk of bias, and each

study was signed by three quality grades including A (low risk of bias), B (moderate risk of bias), and C (high risk of bias), which depended on the possibility of bias from low to high. Each study was subjected to a quality assessment by two authors. Discrepancies were resolved by discussion.

Statistical analysis

Statistical analysis was performed and the forest plots were generated using the Review Manager (version 5.0) Software (Review Manager [Computer program], 2008) application. The odds ratio (OR) and the risk ratio (RR) were calculated along with their 95% confidence intervals (CI) for dichotomous outcomes and mean difference (MD) was calculated for continuous outcomes. Statistical heterogeneity among studies was assessed by means of *chi* square and the extent of inconsistency was assessed by the *P* statistic. When $P < 40\%$, heterogeneity was considered as questionably important; 30%－60% was thought to possibly represent moderate heterogeneity; 50%－90% was regarded as possible substantial heterogeneity; and higher than 75% was deemed a considerable level. If there was no heterogeneity in treatment effect among studies, the fixed effects model was appropriate; Otherwise the random-effect model would be more conservative. Descriptive techniques were used when clinical heterogeneity existed and also when no data could be used in statistical analysis. The stability of outcome was tested by sensitivity analysis when necessary.

Results

Literature search

According to the search strategy and the methods of data collection, 254 studies were identified. EndNote X2 Software was used for document management and 158 duplicates were removed. Sixty-one studies were excluded because those did not meet inclusion criteria and had methodological errors. Thirty-five studies were identified after the first choosing reference and were chosen again by reading the full text. Twenty-nine RCTs (Cheng *et al*, 2010; Dong *et al*, 2008; Feng *et al*, 2010; 2009; Fu, 2006; Geng, 2005; Jia *et al*, 2009; Li, Xu, and Xu, 2008; Li and Hu, 2007; Liang, 2008; Liao *et al*, 2007; Lu, Zuo, and Liu, 2006; Nie *et al*, 2010; Qin and Xu, 2000; Tang and Liu, 2010; Wang *et al*, 2008; 2009; Xing, Zhang, and Nie, 2001; Xu, 2009; Xu and Wang, 2010; Yang and Zhu, 2010; Yu, 2003; Zhang, Yue, and Pan, 2008; Zhang *et al*, 2008; 2009; 2010; Zhang, Zhang, and Fu, 2010; Zhou, 1998; Zhou, Xin, and Yang, 2004) with 1831 patients were included based on the inclusion criteria and the data completeness. Fig. 1 and Table 1 show the process to select potentially relevant studies for inclusion in meta analysis.

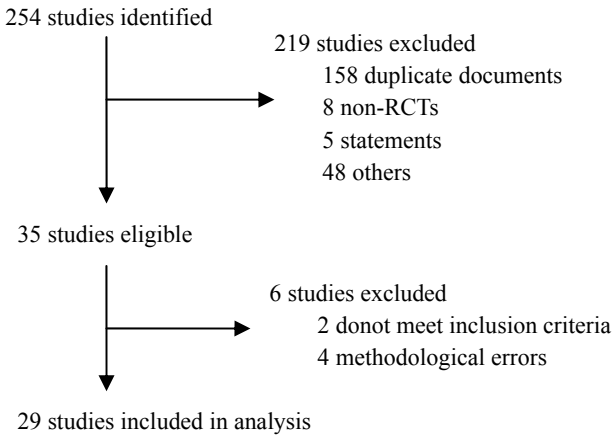

Fig. 1 Selection of trials

Methodological quality of studies

Two trials (Tang and Liu, 2010; Wang *et al*, 2009) involved random digits table and two trials (Liang, 2008; Yu, 2003) used a method of flipping a coin. Remained trials could not legibly describe how the random allocation sequences were generated and the allocations were all said to be "randomized" without exact methods except for two trials (Feng *et al*, 2010; Liao *et al*, 2007) where hospital numbers or treatment order were used. Besides, they could not find out any legible description on allocation sequence in one trial (Zhou, 1998). All the trials did not report whether blinding and allocated concealment were adopted. And those trials had no incomplete outcome data. Moreover, whether other bias existed was unclear. The qualities of these included trials were relatively low. The methodological quality of these included trials is shown comprehensively in Table 2.

Meta analysis results

Twenty-nine studies focus on curative effect and safety of LIC for MPE. It included 1831 patients, 936 with LIC and 895 with cisplatin alone. All meta analysis results were shown in Tables 3－5.

Near-term curative effect (according to the changes

Table 1 Characteristics of included studies

Included Studies	Cases		Age / Years (average)		Sex (M/F)		Drug dose / mg			Time	Outcome
	L + DDP	DDP	L + DDP	DDP	L + DDP	DDP	L + DDP		DDP		
							L	DDP			
Cheng, 2010	30	30	43－75 (59)	43－75 (59)	37/23		2	60	80	1/week	(1)(2)(3)(6)(7)(8)(9)
Dong, 2008	30	29	35－76	35－76	35/24		5	80	80	1/week	(1)(2)(3)(4)(6)(7)(8)(9)(13)
Feng, 2010	35	35	31.6－78.1	31.6－78.1	38/32		3	60－90	60－90	1/week	(1)(2)(3)(6)(7)(11)
Feng, 2009	30	27	40－70	40－70	32/25		4	40	40	1/week	(1)(2)(3)(4)
Fu, 2006	30	30	33－78 (51)	33－78 (51)	51/39		2	80	80	1/week	(1)(2)(3)(6)(7)(9)
Geng, 2005	31	28	34－75	34－75	39/20		4	60	60	1/week	(1)(2)(3)(6)(7)(8)(9)(12)(14)
Jia, 2009	38	35	38－75 (56)	38－75 (56)	41/32		4	40	40	1/week	(1)(2)(3)(4)(6)(7)(8)(9)
Li, 2008	46	47	35－76 (58)	30－78 (57)	29/17	29/18	2	80	80	1/week	(3)(4)(6)(7)(8)(9)
Li, 2007	28	28	41－91 (64)	41－91 (64)	35/21		2－4	20－40	20－40	1/week	(1)(2)(3)(4)(6)(7)(8)(9)
Liang, 2008	37	37	25－70 (51)	25－70 (51)	34/40		2	80	80	1/3 d	(1)(2)(3)(6)(7)
Liao, 2007	36	36	48－73 (58.2)	43－71 (59.1)	23/13	25/11	4	40	60	1/week	(1)(2)(3)(4)(6)(7)(8)(9)
Lu, 2006	25	23	29－81 (55)	29－81 (55)	26/32		2－4	60	40－80	2/week	(1)(2)(3)(4)(6)(7)(8)(9)
Nie, 2010	22	20	(55)	(55)	29/13		2	60－80	60－80	1－2/week	(1)(2)(3)(6)(7)(8)(9)
Qin, 2000	24	23	40－70 (53.6)	40－70 (53.6)	35/12		4	60	60	1－2/week	(1)(2)(3)
Tang, 2010	32	32	32－75 (54.1)	32－75 (54.1)	51/13		4	60	60	1/week	(1)(2)(3)(4)(6)(8)
Wang, 2009	45	45	32－70 (49)	30－69 (48)	37/8	35/10	1	60	60	1－2/week	(1)(2)(3)
Wang, 2008	40	40	(63.5)	(63.5)	49/31		4－6	50	50	2/week	(1)(2)(3)(6)(7)(8)
Xing, 2001	36	34	28－70 (48.5)	21－71 (49.5)	27/9	25/9	4	60－80	60－80	1－2/week	(1)(2)(3)(4)(6)(7)(9)(13)
Xu, 2009	21	16	(58)	(62)	16/5	12/4	4－6	40－60	60	1/week	(1)(2)(3)(4)(6)(7)(8)(9)(10)
Xu, 2010	52	52	30－72 (49)	30－72 (49)	69/35		4	40－80	40－80	1/week	(1)(2)(3)(6)(7)(9)
Yang, 2010	32	30	42－78	42－78	34/28		4	40	60－80	2/week	(1)(2)(3)(4)(6)(7)(8)(9)
Yu, 2003	32	32	27－69 (51)	27－69 (51)	31/33		2	80	80	1/3 d	(1)(2)(3)(6)(7)
Zhang, 2008	30	29	38－75 (60.7)	38－75 (60.7)	33/26		5	60－80	60－80	1/week	(1)(2)(3)(4)(6)(7)(9)(13)
Zhang, 2009	28	28	38－78 (68)	38－78 (68)	40/16		4－6	40－60	40－60	1/week	(1)(2)(3)
Zhang, 2010	22	21	29－80	29－80	28/15		4	40	60	1/week	(1)(2)(3)(5)(6)(7)(8)(9)
Zhang, 2008	36	26	30－70 (52)	35－68 (50)	12/24	9/17	1	30	30	1/3 weeks	(1)(2)(3)(6)(8)(10)
Zhang, 2010	39	39	26－70 (52)	30－72 (50)	29/10	32/7	2	60	60	2/week	(1)(2)(3)(6)(7)(8)(9)
Zhou, 1998	20	20	53 ± 13	51 ± 14	－	－	4	100	100	1/3 weeks	(1)(2)(3)(5)(6)(7)(8)(9)(12)
Zhou, 2004	29	23	34－76 (56.7)	34－76 (56.7)	45/31		4	60－100	60－100	1－2/week	(1)(2)(3)(4)(6)(8)

(1) CR; (2) PR; (3) CR + PR; (4) increased rate of Karnofsky score; (5) diversification of Karnofsky score after treatment; (6) gastrointestinal reactions; (7) fever; (8) myelosuppression; (9) chest pain; (10) liver function damage; (11) kidney function damage; (12) hair loss; (13) general malaise; (14) stomatitis

of pleural effusion) was shown in Table 3. Meta analysis results showed that compared with cisplatin alone, the combination had a statistically significant benefit in improving CR (RR = 1.69, 95% CI: 1.48, 1.94, $P < 0.000\ 01$), PR (RR = 1.35, 95% CI: 1.20, 1.53, $P < 0.000\ 01$), and CR + PR (RR = 1.49, 95% CI: 1.40, 1.59, $P < 0.000\ 01$).

Quality of life, according to the changes of KPS scale, was shown in Table 4. Meta analysis results showed that compared with cisplatin alone, LIC could improve QOL, that is to say, the combination had a statistically significant benefit in the increased rate of KPS score (RR = 1.58, 95% CI: 1.40, 1.80, $P < 0.000\ 01$). Besides, in the aspect of diversification of KPS score after treatment, KPS (more than 70) showed great impact (RR = 1.80, 95% CI: 1.07, 3.04, $P = 0.03$). Nonetheless, KPS (50－69 and less than 50) have no difference in statistics (RR = 0.72, 95% CI: 0.42, 1.24, $P = 0.23$; RR = 0.48, 95% CI: 0.04, 5.31, $P = 0.55$).

Major adverse reactions were shown in Table 5. Compared with cisplatin alone, LIC could protect patients from a great many of adverse reactions, such as gastrointestinal reactions (OR = 0.43, 95% CI: 0.34, 0.56, $P < 0.000\ 01$), myelosuppression (OR = 0.42, 95% CI: 0.30, 0.59, $P < 0.000\ 01$), chest pain (OR = 0.69, 95% CI: 0.51, 0.95, $P < 0.000\ 01$), and general malaise (OR = 0.21, 95% CI: 0.09, 0.48, $P = 0.0002$). Whereas, when it comes to other indicators, the combination had no statistically significant advantages, such as fever (OR = 1.29, 95% CI: 0.92, 1.82, $P = 0.14$),

Table 2 Methodological quality assessment of included studies

Included studies	Sequence generation	Allocated concealment	Blinding	Incomplete outcome data	Free of selective reporting	Free of other bias	Quality grading
Cheng, 2010	Unclear	Unclear	Unclear	No	No	Unclear	B
Dong, 2008	Unclear	Unclear	Unclear	No	No	Unclear	B
Feng, 2010	Treatment oder	Unclear	Unclear	No	No	Unclear	C
Feng, 2009	Unclear	Unclear	Unclear	No	No	Unclear	B
Fu, 2006	Unclear	Unclear	Unclear	No	No	Unclear	B
Geng, 2005	Unclear	Unclear	Unclear	No	No	Unclear	B
Jia, 2009	No	Unclear	Unclear	No	No	Unclear	C
Li, 2008	No	Unclear	Unclear	No	No	Unclear	C
Li, 2007	Unclear	Unclear	Unclear	No	No	Unclear	B
Liang, 2008	Flip a coin	Unclear	Unclear	No	No	Unclear	B
Liao, 2007	Hospital numbers	Unclear	Unclear	No	No	Unclear	C
Lu, 2006	Unclear	Unclear	Unclear	No	No	Unclear	B
Nie, 2010	Unclear	Unclear	Unclear	No	No	Unclear	B
Qin, 2000	Unclear	Unclear	Unclear	No	No	Unclear	B
Tang, 2010	Random digits table	Unclear	Unclear	No	No	Unclear	B
Wang, 2009	Random digits table	Unclear	Unclear	No	No	Unclear	B
Wang, 2008	Unclear	Unclear	Unclear	No	No	Unclear	B
Xing, 2001	Unclear	Unclear	Unclear	No	No	Unclear	B
Xu, 2009	Unclear	Unclear	Unclear	No	No	Unclear	B
Xu, 2010	Unclear	Unclear	Unclear	No	No	Unclear	B
Yang, 2010	Unclear	Unclear	Unclear	No	No	Unclear	B
Yu, 2003	Flip a coin	Unclear	Unclear	No	No	Unclear	B
Zhang, 2008	Unclear	Unclear	Unclear	No	No	Unclear	B
Zhang, 2009	Unclear	Unclear	Unclear	No	No	Unclear	B
Zhang, 2010	Unclear	Unclear	Unclear	No	No	Unclear	B
Zhang, 2008	Unclear	Unclear	Unclear	No	No	Unclear	B
Zhang, 2010	Unclear	Unclear	Unclear	No	No	Unclear	B
Zhou, 1998	No	Unclear	Unclear	No	No	Unclear	C
Zhou, 2004	Unclear	Unclear	Unclear	No	No	Unclear	B

Table 3 Meta analysis on near-term curative effect

Outcome	Number of included studies	L + DDP		DDP		Heterogeneity		Analysis model	Effect estimate	
		Events	Total	Events	Total	*P*	I^2		RR (95% CI)	*P*
CR	28	363	878	210	848	0.63	0	Fixed	1.69 (1.48, 1.94)	< 0.000 01
PR	28	380	890	266	848	1.00	0	Fixed	1.35 (1.20, 1.53)	< 0.000 01
CR + PR	29	773	936	501	905	0.88	0	Fixed	1.49 (1.40, 1.59)	< 0.000 01

liver function damage (OR = 0.98, 95% CI: 0.21, 4.62, *P* = 0.98), and hair loss (OR = 0.55, 95% CI: 0.22, 1.34, *P* = 0.19).

Kidney function damage and stomatitis were shown in Table 5.

These two indicators could not be merged, so they were described separately. The results were as follows: Only one paper (Zhang and Qu, 2008) mentioned kindey

Table 4 Meta analysis on quality of life (KPS)

Outcome	Number of included studies	L plus DDP		DDP		Heterogeneity		Analysis model	Effect estimate	
		Events	Total	Events	Total	*P*	I^2 / %		RR (95% CI)	*P*
Increased rate of KPS score	13	258	367	153	342	0.99	0	Fixed	1.58 (1.40, 1.80)	< 0.000 01
Diversification of KPS score after treatment										
more than 70	2	24	42	13	41	0.35	0	Fixed	1.80 (1.07, 3.04)	0.02
50－69	2	14	42	19	41	0.55	0	Fixed	0.72 (0.42, 1.24)	0.23
less than 50	2	4	42	9	41	0.06	73	Random	0.48 (0.04, 5.31)	0.53

Table 5 Meta-analysis on adverse reactions

Outcome	Number of included studies	L + DDP		DDP		Heterogeneity		Analysis model	Effect estimate	
		Events	Total	Events	Total	*P*	I^2/%		OR (95% CI)	*P*
gastrointestinal reactions	25	178	849	279	812	0.30	11	Fixed	0.43 (0.34, 0.56)	< 0.000 01
fever	22	81	712	62	691	0.22	18	Fixed	1.29 (0.92, 1.82)	0.14
myelosuppression	18	119	557	173	523	0.10	32	Fixed	0.42 (0.30, 0.59)	< 0.000 01
chest pain	18	86	568	110	547	1.00	0	Fixed	0.69 (0.51, 0.95)	0.02
liver function damage	2	4	57	3	42	0.83	0	Fixed	0.98 (0.21, 4.62)	0.98
hair loss	2	22	51	26	48	0.66	0	Fixed	0.55 (0.22, 1.34)	0.19
general malaise	3	9	96	30	92	1.00	0	Fixed	0.21 (0.09, 0.48)	0.0002

function damage, and the data showed that the combination played a role in protecting kidney function (the experimental group: no one suffered from kidney function damage in thirty-five; the control group: two of thirty-five suffered from it). Then, one paper (Geng, 2005) involved stomatitis, and the data displayed that the combination did a good turn in stomatitis (the experimental group: five of thirty-one suffered from kidney stomatitis; the control group: six of twenty-eight suffered from it).

Publication bias

Funnel plot analysis was made for included studies and the result showed asymmetrical funnel plot and publication bias probably occurred. The funnel plot is shown in Fig. 2.

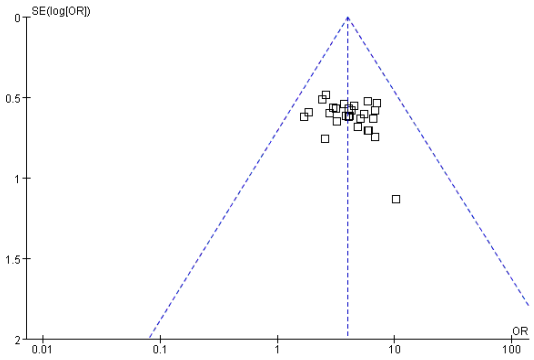

Fig. 2 Result of funnel plot analysis

Discussion

MPE is one kind of common terminal complications which derives from metastasizing or primary tumor of pleural tumor. Approximately, 50% of lung cancer or breast cancer patients suffer from pleural effusion in the process of diseases (Kahn, 2007; Wu *et al*, 2007). High mortality rate appears shocking among MPE patients, and specific data of one-month, three-month, and six-month mortality were 50%, 60%, and 82%－84%, then, the average survival period was 3.1 months (Wu, Zou, and Wu, 2008). Moreover, about 96% of MPE patients suffer from expiratory dyspnea, 56% with chest pain, 44% with cough, and others may have to endure haemoptysis, fever, and voice hoarse which are the signs of terminal tumor (Heffner, Nietert, and Barbieri, 2000). Therefore, LIC has great effects on improving survival rate, quality of life, and prognosis by the means of controlling pleural effusion efficaciously. How to control the pleural effusion

effectively and improve the quality of life? Formerly, they always adopt the method of pure chemotherapy drugs towards pleural perfusion, but curative effect owe ideal.

With extensive clinical application of biological agents, the control rate of pleural effusion could be improved. Currently, commonly used biological reaction regulators in the fields of pleural perfusion therapy are IL-2, lentinan, immunoreactive fibronectin (IFN)-α, TNF-α, and so on. Lentinan is a purified glucan polymer with antitumor activity which is extracted from shiitake mushroom fruiting bodies. Experimental studies have shown that lentinan has no direct cytotoxic effect, works well mainly by enhanced activation of macrophages and killer T cells for host, and induces IFN, and then, it also could enhance the activity of natural killer cells and antibody-dependent cytotoxicity of macrophages in antitumor processing (Hazama *et al*, 1995).

Reviewers read the titles and abstracts comprehensively, and then non-RCTs and case-control studies were excluded. Afterwards, they read the full-text in order to exclude the studies which did not meet the inclusion criteria. The search strategies were widened by the means of tracing reference of included studies for improving scientificity. All studies were comparable because of the same inclusion criteria. Twenty-nine studies included 1831 patients. Through the integration of 29 independent researches, the outcomes of meta analysis were as follows: 1) In the aspect of near-term curative effect (according to the changes of pleural effusion), LIC worked significantly better than the chemotherapy group, and the combination could greatly improve CR and PR. 2) In the aspect of quality of life (according to the changes of KPS scale), the combination had a statistically significant benefit in the increased rate of KPS score, that is, improving the quality of life. Besides, when it comes to the diversification of KPS score after treatment, KPS (more than 70) appeared much more in experimental group than the other, namely, the patients in the combination group were in a better state than chemotherapy group after treatment. 3) In the aspect of adverse reactions, fewer adverse reactions emerged after treatment in the experimental group, such as gastrointestinal reactions, myelosuppression, chest pain, and general malaise. However, when it comes to other indicators, the combination had no statistically significant advantages, such as fever, liver function damage, and hair loss, that is, additional lentinan caused fewer adverse reactions in these indicators. 4) In the aspect of kidney function damage and stomatitis, these two indicators could not be merged, so they were described separately, and the results were as follows: only one paper (Zhang *et al*, 2008) refered to kidney function damage, and the data showed that the combination of lentinan plus cisplatin played a role in protecting kidney function (the experimental group: no one suffered from kidney function damage in thirty-five; the control group: two of thirty-five suffered from it). Then, one paper (Geng, 2005) involved stomatitis, and the data displayed that the combination did a good turn in stomatitis (the experimental group: five of thirty-one suffered from kidney stomatitis; the control group: six of twenty-eight suffered from it).

Most trials could not legibly describe how the random allocation sequences were generated and the allocations were said to be “randomized” without exact method except for two trials (Feng *et al*, 2010; Liao *et al*, 2007) where hospital numbers or treatment order were used. Excellent than others, two trials (Tang and Liu, 2010; Wang *et al*, 2009) involved random digits table and two trials (Liang, 2008; Yu, 2003) used a method of flipping a coin. However, they could not find out any legible description on allocation sequence in one trial (Zhou, 1998). All the trials did not report whether blinding and allocated concealment were adopted. And those trials had no incomplete outcome data. Moreover, whether other bias existed was unclear. All of these told us that it was relatively low strength evidence. However, it is difficult to adopt random allocation sequence and blinding since the particularity of chemotherapy for patients with tumors. Furthermore, all studies were comparable because of the same inclusion criteria and all studies doing consistency analysis before treatment such as age, gender, treatment factors, and so on. In summary, the evidence was worthy of belief.

Taking limitations into account, the first problem was that uncertain method of estimation about sample size and small amount of sample in the majority of trials, thus, it would result in low power of test.

Secondly, dosage and duration of LI were not completely consistent and it would have an effect on final index measured. The third problem appeared that all trials did not definitely describe whether allocated concealment was made. And it was reported that exaggerated therapeutic effects may happen on account of inadequate or even no allocated concealment. Since the subjective index were used, it was important to use blinding for the study of LI treating patients with MPE. If blinding fails to work or insufficiently work, it would result in high implementation bias and measurement bias. Besides, some data were not merged because different statistical data were selected in different trials and it was difficult to reach a unified conclusion. These problems may play very important roles in swaying the reliable conclusion. However, the conclusion of this study was worthy of belief because of high qualities of literatures, but the limitations still need to improve.

Conclusion

In conclusion, this meta-analysis shows that: compared with chemotherapy including cisplatin alone, LIC could significantly improve the near-term curative effect and QOL, and played an active role in adverse reactions after chemotherapy. However, there exists an urgent need for more high-quality, multicenter, adequate randomized, controlled clinical trials for LIC in the treatment of MPE.

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