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REVIEW – CLINICAL ONCOLOGY

Lentinan as an immunotherapeutic for treating lung cancer: a review of 12 years clinical studies in China

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Abstract

Purpose Lentinan is a polysaccharide extracted from *Shiitake* mushrooms that have been used to improve general health for thousands of years in Asia. Lentinan injection is a clinically approved drug in several countries in Asia. The purpose of this study is to review the structure, preclinical and clinical studies, and molecular mechanisms of lentinan. Most importantly, the clinical effectiveness of lentinan as an adjuvant therapeutic drug in treating patients with lung cancer in China during the past 12 years is analyzed statistically.

Methods We carried out literature search of randomized controlled trials (RCTs) published from 2004 to 2016 based on CNKI (China National Knowledge Infrastructure), VIP (Chongqing VIP Chinese Scientific Journals Database) and Wanfang database, and 38 eligible RCTs of lentinan-associated lung cancer treatment were identified, containing 3,117 patients.

Results The structure and function relationship and underlying molecular mechanism of lentinan as an immunostimulant has been summarized. The mean value of overall response rate in treating lung cancer was increased from 43.3% of chemotherapy alone to 56.9% of lentinan plus chemotherapy [$p < 0.001$, 95% confidence interval (CI) 0.102–0.170]. Compared with chemotherapy alone, lentinan plus chemotherapy showed more efficacy in treating lung cancer (pooled RR 0.79, 95% CI 0.74–0.85) and no statistical heterogeneity was found among studies ($I^2 = 11\%$).

Conclusion Clinical data presented in the past 12 years shows that lentinan is effective not only in improving quality of life, but also in promoting the efficacy of chemotherapy during lung cancer treatment.

Keywords Cancer · Chemotherapy · Immunobalance · Immunostimulant · Lentinan

Background

In 2012, according to the World Health Organization (WHO), there are about 8.2 million cancer deaths, or 14.6% of deaths worldwide; lung cancer being the deadliest form (Forman and Ferlay 2014; The Top 10 Causes of Death 2018). Progress has been made in cancer treatment (Banin Hirata et al. 2014), but there are still no effective drugs for treating most types of solid cancers (Li 2001). Despite low effectiveness, chemotherapy and radiation therapy are still major treatments for cancer patients (Thomas et al. 2014). Patients have to face severe side effects, and for breast and non-small cell lung cancer, the 5-year survival rate is less than 50% (Barrett 2010; Makanjuola et al. 2014; Schiller et al. 2002). Thus, reducing side effects of cancer treatment and enhancing the quality of life for cancer patients are crucial.

The medicinal qualities of *Shiitake* mushrooms have been known for thousands of years in China (Chen and Seviour 2007; Chen and Raymond 2008). The anti-tumor property of lentinan was reported by Chihara et al. (1969). Lentinan is mainly composed of β-glucan with anti-tumor, anti-inflammatory (Ruthes et al. 2016), anti-diabetes properties (Wang et al. 2016), and other therapeutic properties. Lentinan was approved as an adjuvant for stomach cancer therapy in Japan in 1985. It is

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approved for treating multiple types of cancer, hepatitis, and other diseases in China. Lentinan is available as capsules, tablets, and injections. The capsules and tablets of lentinan is taken orally as a traditional medicine. Intravenous injection of lentinan is clinically approved and used in hospital with a dose of 1–1.5 mg/day/patient. Clinical data show that lentinan is a biological response modifier and an immunostimulant with proven efficacy in treating hepatitis (Wang 1994; Wu et al. 1993), HIV (Gordon et al. 1998), malignant pleural effusion (Yoshino et al. 2010; Chang et al. 2013) and cancers (Ina et al. 2013; Wang et al. 2012).

Structure of lentinan

There have been numerous reports on structures and components in lentinan, but only β-glucan has been established to be associated with immunologic competence (Murphy et al. 2010). The primary structure of β-glucan in lentinan was demonstrated in 1977 (Saitô et al. 1977), which consists of a β-(1–3)-glucose backbone with two (1–6)-β-glucose branches of every five glucose units (Lv et al. 2009) (Fig. 1). The secondary structure of β-glucan is a single helical conformation confirmed by ^{13}C-NMR (Lv et al. 2009). Surenjav et al. (2006) studied four types of polysaccharides extracted from *Lentinus edodes* (fruiting body). All of them are β-glucans containing 4.6–15.2% proteins and displaying anti-tumor activities. However, the activity is reduced after the polysaccharides are processed by ultrasound and deproteinization. This indicates that the secondary structure, relative molecular mass, and associated proteins may also affect the anti-tumor activities of lentinan.

Immunostimulatory mechanisms of lentinan

Studies (Brown and Gordon 2003) show that β-glucan as the main component of lentinan plays a key role in immunoregulation of lentinan. It can trigger downstream signaling, such as MAPK-NFκB and Syk-PKC, through binding with pattern recognition receptors (TLR2/4/6/9, Dectin-1, etc.), the complement receptor (CD11b), and other membrane receptors (Zhou et al. 2014), which activates the function of immunocytes (NK, macrophage, T cells) (Dai and Wu 1998; Liu et al. 2003). Peng et al. (2008) used lentinan (self-made) to stimulate mouse spleen lymphocytes and the results showed that the expression of both TLR4 and TLR9 are up-regulated initially in addition to up-regulated TNF-α expression by T-lymphocytes. Wang et al. (2008) reported that lentinan (Zhejiang Fangge Pharmaceutical CO., LTD) promotes IgG secretion by B-lymphocytes and enhances phagocytic activity of macrophages in mice. Peter et al. (1988) showed that lentinan (self-made) activates natural killer cells (NK) and induces antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro. Additionally, Kupfahl et al. (2006) reported that pre-treatment of mice with lentinan (self-made) results in increased concentrations of TNF-α, IL-12 and IFN-γ (Fig. 2). Yoshino et al. found that the percentage of CD4+ IFN-γ+ T cell increases significantly ($p < 0.05$) whereas the percentages of CD4+ IL-4+ T cell and CD4+ IL-6+ T cell decreases significantly ($p < 0.02$) in patients' blood with digestive cancers after intravenous administration of lentinan, which indicates that lentinan can reverse the Th2-dominated immune microenvironment of cancer patients, and enhance the ratio of CD8+ T cells and Th1 cells in the whole T cell subgroups (Yoshino et al. 2000; Wang et al. 2010).

Another significant influence of lentinan in regulating immunity may be due to "trained immunity", which was

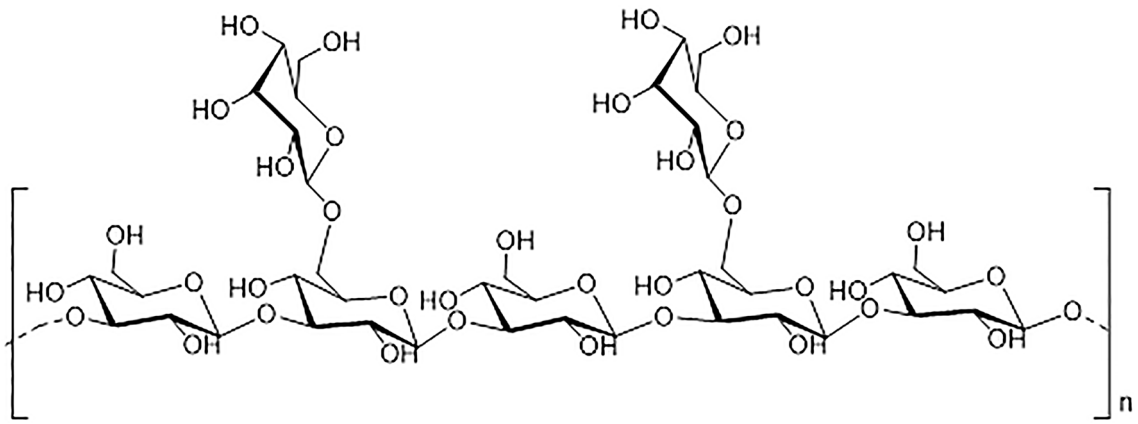

Fig. 1 A schematic diagram of β-glucan structure in lentinan. Glucose units are linked through β-(1–3) glycosidic bond to form backbone with β-(1–6) glucose branches

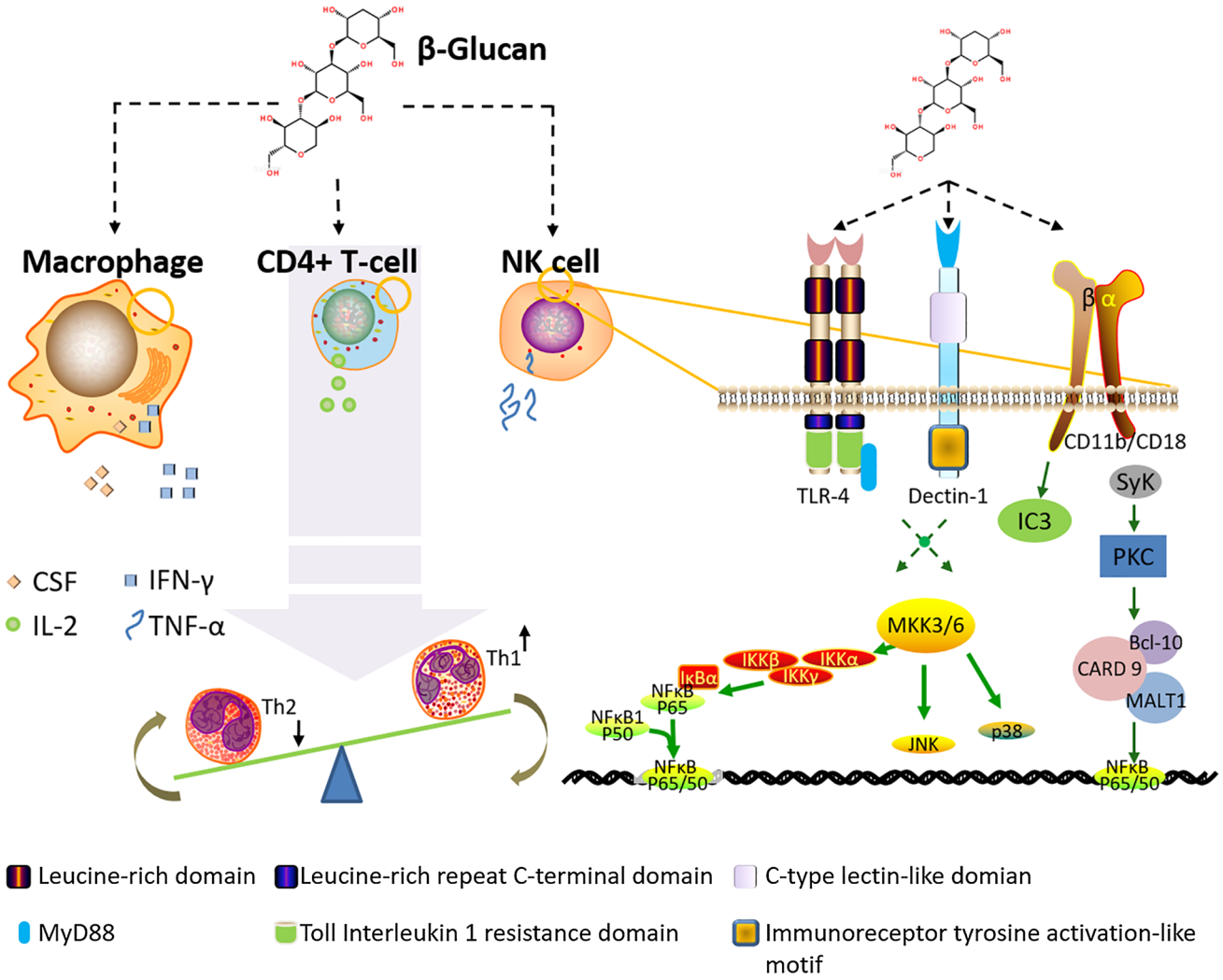

Fig. 2 Immunostimulating and immunobalancing effects of β-glucan. Immunocytes can be activated by β-glucan through binding with membrane receptors, such as pattern recognition receptors (TLR4, Dectin-1), complement receptor (CD11b), etc. Subsequently, downstream signaling pathways, MAPK-NFκB and Syk-PKC-NFκB, are involved in immunoregulation

firstly described as triggered by human pathogen *Candida albicans* (Quintin 2018). As a major component of fungi, β-glucan functions as a stimulus to induce a non-specific memory resulting in an enhanced immune status. Once cells of the innate immune compartments such as monocytes or natural killer (NK) cells encounter a secondary stimulus, an optimal response will be triggered. Studies have shown that trained immunity can improve host defense and result in a better survival (Bekkering et al. 2016; Quintin et al. 2012). The potential molecular mechanisms underlying the induction of innate immune memory by β-glucan is a complex interaction between immunological, metabolic and epigenetic changes. Cheng et al. found that oxygen consumption of monocytes shifted from oxidative phosphorylation to aerobic glycolysis after treating with β-glucan (Cheng et al. 2014). Additionally, β-glucan affects the tri-methylation of the lysine 4 on the histone 3 (H3K4), and reverses the epigenetic state of LPS-induced immunological tolerance (Novakovic et al. 2016).

Cytotoxicity of lentinan

Lentinan can also possess direct cytotoxicity on tumor cells. Bao et al. proved that lentinan could trigger apoptosis through intracellular reactive oxygen species (ROS) while treating human bladder cancer T24 cells (Bao et al. 2015). Similarly, it has been reported that lentinan induced cytotoxicity on S180 cells via mitochondria pathways by up-regulating Bax and down-regulating Bcl-2, which resulted in apoptosis of S180 cells (Zhang et al. 2015a).

Preclinical studies of combination of lentinan with chemotherapy and targeted therapy

Lentinan has been proved to function as a biological response modifier (BRM) during preclinical pharmacological studies (Wang et al. 2015; Nishitani et al. 2013; Xu et al. 2011). It exhibits a great potential to boost immune response to tumor burden. Oncologists realize that such an effective but low toxic immunomodulator is an ideal agent to combine with chemotherapeutics due to the severe side effects and immunosuppressive environment caused by chemotherapy. For treating non-small cell lung cancer (NSCLC), lentinan was found to be synergistic with paclitaxel by activating TXNIP-NLRP3 inflammasome through the ASK1/p38 MAPK signal pathway (Liu et al. 2015). Cisplatin is the first-line drug in treating advanced lung cancer. However, nephrotoxicity is the complication caused by cisplatin. A new study showed that lentinan significantly prevented cis-DDP-induced kidney injury in vivo through activation of the NRF2-ARE signaling pathway (Chen et al. 2016).

Furthermore, targeted therapies that specifically inhibit the growth of cancer cells have been developed greatly (Carter 2001; Clynes et al. 2000). HER2 is a member of the ErbB family that plays an important role in promoting oncogenic transformation and tumor growth (Slamon et al. 1987). Herceptin (trastuzumab) has been successfully used in treating HER2 overexpressed breast cancer patients (Hamy et al. 2018). An in vivo study clearly demonstrated that lentinan significantly suppresses tumor growth combined with Herceptin in BT474 xenografts in nude mice (Cheung et al. 2002). Considering that in approximately 18–33% NSCLC tumors, 17–42% adenocarcinomas, and 2–40% large-cell carcinomas lung cancer demonstrate overexpressed HER2 (Hirsch et al. 2002), the synergistic action with targeting cancer therapy might be expected when lentinan is used in combination with antibodies plus cytotoxic chemotherapeutic agents for patients with HER-2 positive lung cancer.

Clinical effects of lentinan verified by statistical analysis

To explore the effects of chemotherapy plus lentinan (C + L) comparing to that of chemotherapy alone (L), we searched all published clinical studies of lentinan in treating lung cancer during the past 12 years (2004–2016) in China. Our search was conducted using CNKI, VIP and Wanfang databases with the terms of "lung cancer", "lung neoplasms", "lentinan", "chemotherapy" and "randomized controlled trials (RCTs)". Qualified RCTs should report the relative risk (RR) and the corresponding 95% confidence intervals (CIs) or sufficient information to calculate them. As a result, 38 RCTs containing 3117 patients were identified.

Our statistical analyses were conducted by REVMAN Software (version 5.1.2; The Cochrane Collaboration, Oxford, UK) and SPSS (version 19, IBM, Chicago, US). A pooled relative risk (RR) was produced with 95% CIs to summarize the effect of each comparison tested, using a random effects model as a conservative estimate. Global statistical heterogeneity across all comparisons was assessed using the I^2 measure from the 'netmeta' statistical package. The I^2 measure ranges between 0 and 100% and is typically considered low, moderate and high for values of 25–9, 50–74 and ≥ 75%, respectively (Table 1).

Response rates (RR) known as common evaluation indicator of tumor treatment is the sum of complete response (CR) and partial response (PR). Response rate for chemo (C) or chemo + lentinan (C + L) treated patients are summarized and shown in Table 2 with the p values calculated and indicated for each RCT. The reported overall response rates in C + L groups improved significantly compared to C groups (mean value 56.9 vs 43.3%, $p < 0.001$, 95% CI 0.102–0.170). C + L therapy showed more efficacy in treating lung cancer (pooled RR 0.79, 95% CI 0.74–0.85) and no statistical heterogeneity was found among studies ($I^2 = 11\%$) (Fig. 3). Above analyses indicate that lentinan is effective not only on improving quality of life but also on promoting the efficacy of chemotherapy during lung cancer treatment.

The side effects of lentinan

Although the side effects of lentinan is rare, some clinical cases reported complications (Table 3). Low blood pressure, allergy, urgent appeal, and dizziness were the major side effects. Usually, these symptoms would resolve within 15–30 min after drug withdrawal, oxygen uptake, intravenously given 10 mg dexamethasone, or intravenously given 10 ml 10% calcium gluconate. These cases indicate that more observation during nursing is required for the drug, as they have not been tested for anaphylaxis in advance, and only that can avoid serious consequences in time.

Discussion

This article briefly introduced the structure and molecular mechanisms of lentinan in treating lung cancer. Edible mushrooms have been used as traditional herbal medicine in China for thousands of years and it is known to enhance

Table 1 List of abbreviations

Abbr.	Full name	Abbr.	Full name
Drugs			
5-Fu	5-Fluorouracil	IFO	Ifosfamide
ADM	Adriamycin	L-OHP; OX	Oxaliplatin
CAPE	Capecitabine/xeloda	MA	Megestrol acetate
CBP	Carboplatin	MMC	Mitomycin
CF	Leucovorin; calcium folinate	NDP	Nedaplatin
Chemo	Chemotherapy	NVB	Vinorelbine
CS	Cefalothin sodium	PDN	Prednisone
CTX	Adenosine cyclophosphate	PTX	Paclitaxel; taxinol
DDP	Cisplatin; diamminedichloroplatinum	S-1	Tegafur gimeracil oteracil
DXL	Docetaxel; taxotere	THP	Pirarubicin
EPI	Epirubicin	VCR	Vincristine
FT	Tegafur/futrafur	VP-16	Etoposide
GEM	Gemcitabine	YS	Yanshu injection
Drug combinations for chemo			
CAF	CTX + ADM + 5-Fu	GP	GEM + DDP
CAP	CTX + ADM + DDP	IEP	IFO + VP-16 + DDP
CF	CF + 5-Fu	LFP	CF + 5-Fu + DDP
CFOXFT	CF + L-OHP + FT	MAFP	MMC + ADM + 5-Fu + CBP
CHOP	CTX + ADM/THP + VCR + PDN	MATP	MA + PTX + DDP
DCF	DXL + DDP + 5-Fu	MFP	MMC + 5-Fu + DDP
DF	DXL + 5-Fu	NOX	NVB + L-OHP
DOX	DXL + L-OHP	NP	NVB + DDP
DP	DXL + DDP	OF	L-OHP + 5-Fu
ECF	EPI + DDP + 5-Fu	PC	CBP + PTX
ELF	VP-16 + CS + 5-Fu	PCF	PTX + DDP + 5-FU
ELFP	VP-16 + CS + 5-Fu + DDP	PF	PTX + 5-Fu
EOF	EPI + L-OHP + 5-Fu	PN	PTX + NDP
EOX	EPI + L-OHP + CAPE	SOX	S-1 + L-OHP
EP	VP-16 + DDP	SP	S-1 + DDP
FAC	5-FU + ADM + CTX	TA	PTX + ADM
FOLFOX	CF + 5-Fu + L-OHP	TACE	EPI + MMC + CBP
FOLPCF	CF + PTX + DDP + 5-Fu	TP	PTX + DDP
FP	5-Fu + DDP	XELOX	L-OHP + CAPE
FTP	FT + DDP	XrayDP	X-Ray + DXL + DDP

body's immunity. Pharmacological studies show that lentinan is the major biological component in mushrooms. Clinical data presented in the past 12 years show the effect of lentinan on improving quality of life and on promoting the efficacy of chemotherapy and radiation therapy during lung cancer treatment.

Even though it shows cytotoxicity on cancer cells in vitro, lentinan functions mainly as an immune system modulator. The immune system modulator is the earliest method used in cancer treatment that can be dated back to 1892 (Levine 2008). Compared to current immunotherapies, such as immune checkpoint inhibitors (like PD1/PD-L1, CTLA-4), adoptive T-cell therapies (like CAR-T, TCR-T), antibody-dependent treatments (like trastuzumab, rituximab) and cancer vaccines (like HPV-vaccine, Provenge), the anti-tumor effect of lentinan is non-specific and wide spectrum. It is always used as an adjuvant therapy in treating cancer. In the future, the combination of non-specific and specific immunotherapies or the use of different immune system regulators is worth exploring.

Presently, the ability of immunoregulation has drawn more attraction to oncologists and pharmacologists. Imbalance of Th1/Th2 and immunosuppressive tumor microenvironment caused by chemo have been found to be an important reason for failure of chemotherapy (van Meir et al. 2017; Zheng et al. 2017). Accordingly, chemoimmunotherapy has been used to address the shortcomings of chemotherapy (Kay et al. 2017; Ina and Furuta 2017). Glycan-based drugs,

Table 2 Response rate for chemo (C) or chemo + lentinan (C + L) treated patients with lung cancer

Cases (M/F)	Age	C group cases (M/F) drugs used		C + L group cases (M/F) drugs used		Dosage and administration of lentinan	Duration (weeks)	(C + L)/C (%) response rate	References
112 (75/37)	35–71	56 (38/18)	XrayDP	56 (37/19)	L + XrayDP	1 mg/d, i.v	4	88.7/83.3	Bai (2010)
60 (39/21)	55 ± 3	30 (20/10)	GP	30 (19/11)	L + GP	1 mg/d, i.v	4	86.7/76.7	Yin and Yang (2016)
46 (29/17)	59[a]	20 (12/8)	DDP	26 (17/9)	L + DDP	1 mg/d, i.v	6	84.6/55.0*	Lu (2013)
140 (78/62)	60–85	70 (38/32)	GP/TP	70 (40/30)	L + GP/TP	1.5 mg/d, i.v	8	82.9/62.9*	Zhang (2016)
49	N/A	26	EP	23	L + EP	1 mg/d, i.v	6	76.9/39.1**	He et al. (2015)
104 (54/50)	33–73	52 (27/25)	NP	52 (27/25)	L + NP	1.5 mg/d, i.v	6	71.2/44.2*	Ma (2014)
86 (44/42)	N/A	42 (25/17)	NP	44 (28/16)	L + NP	1.5 mg/d, i.v	8	70.5/69.0	Ding et al. (2012)
98 (65/33)	60 ± 13	49 (34/15)	GP	49 (31/18)	L + GP	1.5 mg/d, i.v	4	69.4/55.1*	Li et al. (2016)
139 (80/59)	60–86	70 (38/32)	TP/GP	69 (42/27)	L + TP/GP	1.5 mg/d, i.v	6	66.7/60.0	Zhang et al. (2015b)
87 (57/30)	66 ± 14	46 (32/14)	EP	41 (25/16)	L + EP	1.5 mg/d, i.v	6	65.9/43.5**	Song and Zhu (2016)
68 (42/26)	25–78	34	GP	34	L + GP	1.2 mg/d, i.v	8	64.7/47.1*	Dai (2014)
62 (38/24)	38–69	31 (18/13)	GP	31 (20/11)	L + GP	1 mg/d, i.v	8	64.5/38.7*	Li et al. (2009)
61 (39/22)	39–74	30 (20/10)	GP	31 (19/12)	L + GP	1 mg/d, i.v	5	64.5/36.7*	Zhao and Ma (2011)
66 (37/29)	N/A	32 (18/14)	DP	34 (19/15)	L + DP	1 mg/d, i.v	4	61.7/31.2*	Qian (2010)
65 (51/14)	43–71	32 (26/6)	CAP + CE	33 (25/8)	L + CAP + CE	1 mg/d, i.v	4	57.6/34.4*	Chai and Xiao (2005)
231 (146/85)	60 ± 14	105 (68/37)	GP	126 (78/48)	L + GP	1 mg/d, i.v	6	57.1/40.0*	Wu (2015)
52 (31/21)	45–78	22 (13/9)	GP	30 (18/12)	L + GP	1.5 mg/d, i.v	6	33.3/54.5*	Li et al. (2013)
52 (37/15)	55–75	26 (20/6)	PC	26 (17/9)	L + PC	1 mg/d, i.v	8	53.8/42.3	Dai (2010)
63 (38/25)	43–71	31	NP	32	L + NP	1.5 mg/d, i.v	8	40.6/48.4	Lu et al. (2008)
68	32–74	34	GP/NP/TP	34	L + GP/NP/TP	1 mg/d, i.v	4	52.9/44.1	Zhao (2012)
100 (72/28)	25–80	50	GP	50	L + GP	1 mg/d, i.v	5	52.0/28.0**	Zhu and Zhang (2013)
90 (62/28)	≤ 75	45 (30/15)	GP/NP/DP	45 (32/13)	L + GP/NP/DP	1 mg/d, i.v	6	51.1/28.9**	Zhao et al. (2011)
76 (51/25)	40–60	38 (25/13)	MATP	38 (26/12)	L + MATP	1.5 mg/d, i.v	6	50.0/47.4	Xie et al. (2006)
78 (66/12)	34–71	26 (22/4)	NOX	52 (44/8)	L + NOX	1.5 mg/d, i.v	4	50.0/46.1	Shang and Huang (2009)
81 (65/16)	18–60	39 (32/7)	NP	42 (33/9)	L + NP	1 mg/d, i.v	2	50.0/33.3**	Wang et al. (2006)
98 (64/34)	26–78	49	GP	49	L + GP	1 mg/d, i.v	4	49.0/40.8	Jiang et al. (2010)
70	32–72	35	GP/NP/DP	35	L + GP/NP/DP	1.5 mg/d, i.v	4	48.6/40.0	Jiang and Zhou (2009)
64 (55/9)	35–69	31 (27/4)	NP	33 (28/5)	L + NP	1.2 mg/d, i.v	6	48.5/35.5*	Shi et al. (2007)
61 (45/16)	65–85	29 (22/7)	NP	32 (23/9)	L + NP	1 mg/d, i.v	8	46.9/34.5*	Wu (2009)
69	N/A	34	GP	35	L + GP	1 mg/d, i.v	6	45.7/41.2	Zhang et al. (2014)
68 (39/29)	35–76	35	PC	33	L + PC	1 mg/d, i.v	4	45.5/45.7	Yue and Jia (2010)
113 (68/45)	42–76	56	DP	57	L + DP	1.5 mg/d, i.v	5	43.9/37.5	Zhang et al. (2009)
80 (58/22)	33–74	40 (30/10)	NP	40 (28/12)	L + NP	1 mg/d, i.v	6	42.5/45.0	Xin et al. (2016)
82 (63/19)	51 ± 4	42 (33/9)	GP	40 (30/10)	L + GP	1.5 mg/d, i.v	8	42.5/41.5	Wang et al. (2011)
86 (55/31)	43–72	43 (26/17)	DP	43 (29/14)	L + DP	1.5 mg/d, i.v	8	37.2/16.3*	Wei and Xie (2015)
71(50/21)	26–74	36 (26/10)	GP	35 (24/11)	L + GP	1 mg/d, i.v	6	37.1/36.1	Zhao et al. (2013)
51 (29/22)	56–58[a]	26 (14/12)	GP	25 (15/10)	L + GP	1 mg/d, i.v	4	36.0/34.6	Han et al. (2012)
80 (53/27)	18–70	40 (28/12)	DP	40 (25/15)	L + DP	1 mg/d, i.v	6	30.0/15.0*	Xiao et al. (2015)

N/A not available

**$p < 0.01$, *$p < 0.05$, Student's *t* test

[a]Median

such as lentinan, are potential and ideal immunoregulating drugs that can be combined with chemotherapeutics due to their broad spectrum of therapeutic properties, relatively low toxicity, and low costs. In fact, other types of tumors have been treated with lentinan and chemotherapeutics. For example, a phase III study comparing therapy using S-1/lentinan with S-1 alone is now underway in Japan (Ina et al. 2011). We deem that these clinical experiences may be helpful in treating lung cancer in future and increasing full use of lentinan for cancer patients worldwide.

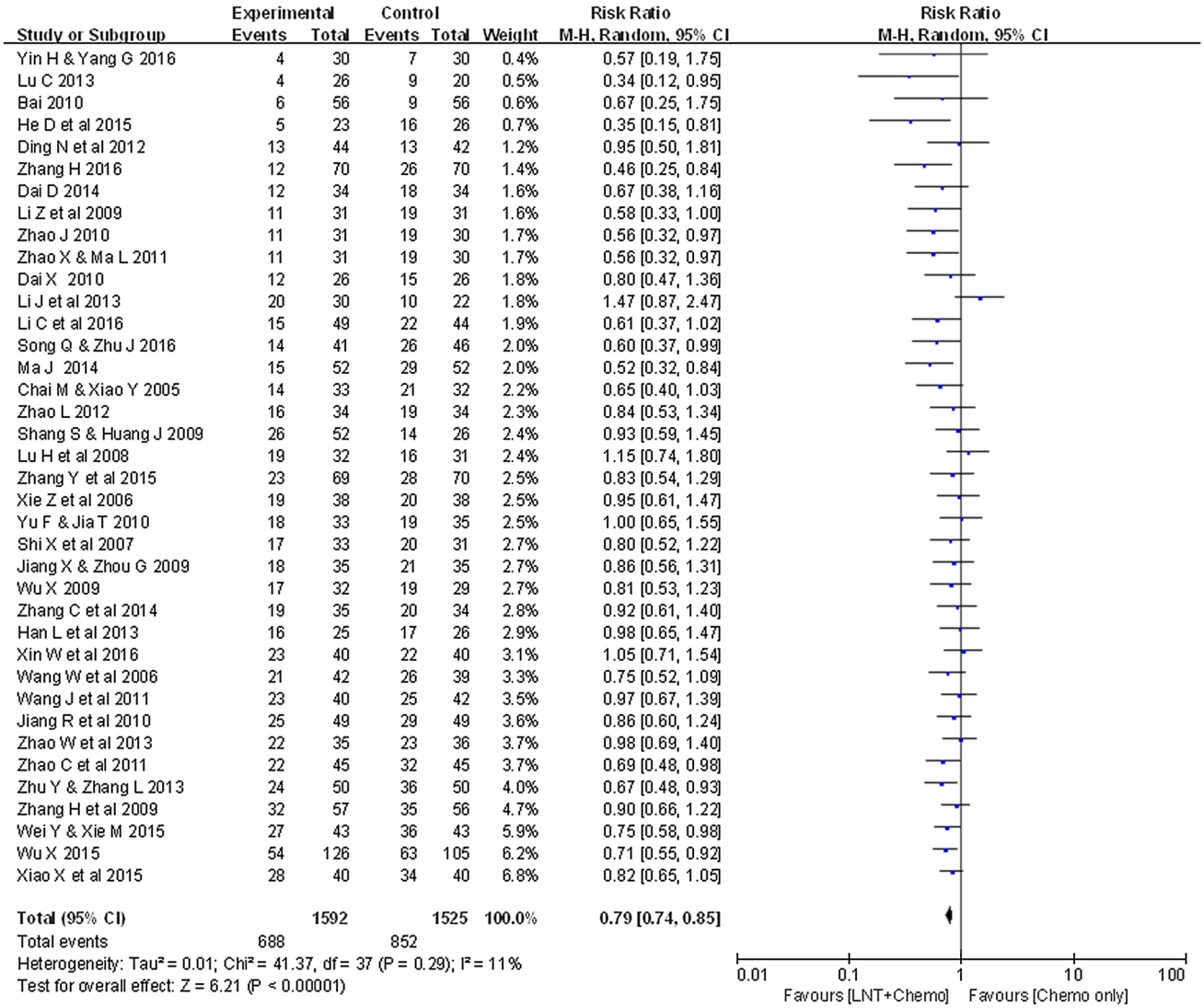

Fig. 3 Forest plot of summary relative risks (RRs) of lentinan-associated chemotherapy and chemotherapies. Lentinan adjuvant therapy was ranked more effective in treating lung cancer (RR 0.79, 95% CI 0.74–0.85). I^2 for global statistical heterogeneity = 11%

Table 3 Lentinan-associated adverse reactions in treating lung cancer

Cases (M/F)	Age	Adverse events	References
14 (8/6)	36–82	Low blood pressure, allergic shock	Zhou and Liu (2010)
1 (1/0)	51	Chest tightness, palpitation, dyspnea, blurred mind, hypotension	Deng et al. (2010)
3 (1/2)	46–56	Dizziness, low blood pressure, chilly	Peng et al. (2013)

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Compliance with ethical standards

Conflict of interest Authors declare no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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