Intrathoracic infusion therapy of thymic peptides and chemical irritants for malignant pleural effusion: a meta-analysis of 24 randomized controlled trials

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Abstract

Background: To further determine the clinical efficacy and survival of intrathoracic infusion with TPs and chemical irritants and their therapeutic threshold and optimal control regimen to achieve a desired response in malignant pleural effusion (MPE).

Methods: We collected all randomized controlled trials (RCTs) of TPs with chemical irritants from Chinese and English databases (from inception until September 2019), and performed a new meta-analysis following the PRISMA guidelines. We measured their bias risk, summarized data using meta-analysis, and evidence quality using the Grades of Recommendation Assessment, Development and Evaluation approach.

Results: We collected 24 trials involving three TPs and platinum and 1,592 patients. Most trials had unclear bias risk. TPs with platinum significantly improved complete response [4.02 (3.12 to 5.18)] and quality of life [3.64 (2.34 to 5.66)], the 0.5-year overall survival (OS) rate [5.75 (3.02 to 10.92)], and 1-year OS rate [5.29, (1.71 to 16.36)], and reduced the treatment failure, myelosuppression, and gastrointestinal toxicity. For patients with moderate to large volume of pleural effusion, KPS score ≥ 50 to 60, or AST ≥ 3 months, the thymosin (200–300mg/time), thymopentin (2mg/time) or thymosin alpha 1 (3.2mg/time) with cisplatin (30–40mg/m²), carboplatin (400mg/m²), or oxaliplatin (100mg/m²) are possible regimens for achieving a desired success, and low failure. Most results were robust and moderate quality.

Conclusion: The moderate evidence suggests that the TPs with platinum is beneficial to the patient with MPE, and provides evidence for the therapeutic threshold and possible regimens that may achieve a desired success and reduce the failure.

Background

Malignant pleural effusion (MPE), often originates from most malignant tumors, is a common and challenging problem. Patients often suffer from breathlessness, poor quality of life (QOL) and prognosis [1–2]. Control of the effusion significantly reduces morbidity, and improves quality of life. Chemical pleurodesis is a first-line intervention for MPE without a nonexpendable lung (NEL) [3]. After draining effusion, a chemical irritant such as talc poudrage [4], tetracycline [5], bleomycin [6], cisplatin (DDP) [7], doxycycline [8], or silver nitrate [9], among others is instilled into the pleural cavity to induce intrapleural inflammation and fibrosis, and then improve clinical symptoms. However, intrathoracic infusions of chemical irritants remain palliative, with a median survival ranging from 3 to 12 months [10–11]. Thus, developed new control strategies are utterly important.

Biological response modifiers (BRMs) have purported important biological activities as anti-tumor, anti-infection, and immunomodulation [12–13]. As important BRMs, thymic peptides (TPs) included the purified thymus extracts (pTE) as thymosin extracted from thymus, and the synthetic thymic peptides (sTP) as thymosin alpha 1 (Ta1) and thymopentin. Ta1, a 28-amino acid peptide, and thymopentin, a five-peptide were first described and characterized from calf thymuses in 1977[14] and 1979 [15–16], respectively. Owing to their pleiotropic biological activities, TPs has been used in the treatment of cancers and infectious diseases in clinic [17–20]. Our previous systematic review and meta-analysis [21] found that the sTP, especially Ta1 with chemotherapy might improve anti-tumor immunity, tumor responses, QOL, and 1- year overall survival (OS) rate, and result in a low incidence rate of neutropenia, thrombocytopenia and gastrointestinal reactions. However, can intrathoracic infusion therapy of TPs and chemical irritants improve clinical efficacy and survivals of the patients with MPE? A previous meta-analysis [22] reported that thymosin combined with oxaliplatin might improve the clinical response and host immunity, and decrease the incidence of adverse drug reactions (ADRs) in lung cancer with MPE. However, they did not conclusively determine whether administration of the TPs with chemical irritants improves the clinical response, survival, and reduces the ADRs. Additionally, their therapeutic threshold and optimal control regimen to achieve a best possible clinical response and desired safety have yet to be determined.

So far, new original studies [23–25] have been published. Therefore, the aim of this meta-analysis was to further determine the clinical efficacy and survival of intrathoracic infusion with TPs and chemical irritants, and their therapeutic threshold and optimal control regimen to achieve a best possible clinical response and desired safety, and to provide an optimal evidence for developing an individualized control strategy based on TPs and chemical irritants for MPE.

Materials And Methods

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [26], we designed, performed and reported a meta-analysis about intrathoracic infusion therapy of TPs and chemical irritants in MPE.

Inclusion And Exclusion Criteria

All eligible studies must meet following criteria. All subjects had malignant tumors with MPE, which was diagnosed following thorax imaging, pleural fluid analysis, cytology, or pleural biopsy. All patients had no limitations on the primary tumors, and thoracentesis or indwelling pleural catheters (IPCs). Before intrathoracic infusion therapy, all patients had normal liver, kidney, and heart function. The intervention studied was TPs administered via intrapleural infusion, and not the subcutaneous, intravenous, or intramuscular injection. The experimental group was administered TPs with chemical irritants, and the control group was administered chemical irritants alone. One month before therapy, no patients received intrapleural infusion using chemical irritants, other BRMs, traditional Chinese medicine (TCM), or hyperthermia. The primary outcomes were treatment success, treatment failure, and survival, and the secondary outcomes were QOL, peripheral blood lymphocytes, ADRs, and thoracentesis-related adverse events (TRAEs). All studies were randomized controlled trials (RCTs), and no restrictions on follow-up protocols or research institutions.

All un-eligible studies must meet the following criteria: duplicates; studies of non MPEs, and non TPs therapy; studies of TPs alone or plus other BRMs, TCM, hyperthermia, or systemic chemotherapy; meeting abstracts, reviews without specific data, and irrelevant systematic reviews or meta-analyses; cohort, case

control, single arm studies, or case reports; studies without data on treatment success, treatment failure, survival, peripheral blood lymphocytes, QOL, ADRs, or TRAEs.

Search Strategy

Two reviewers (Cheng-Qiong Wang and Min He) independently searched all studies of thymic peptides with chemical irritants in MPE from Chinese and English electronic databases (from inception until September 2019) as PubMed, Embase, Web of Science, China National Knowledge Infrastructure Database (CNKI), Chinese Scientific Journals Full-Text Database (VIP), Wanfang Database, China Biological Medicine Database (CBM), and Cochrane Central Register of Controlled Trials (CENTRAL, Issue 9 of 12, September 2019). We developed retrieval strategies using MeSH and free word. The retrieval form was ("Pleural Effusion"[Mesh] OR Pleural Effusion OR Pleural Effusions OR Hydrothorax OR MPEs OR MPE) AND ("Thymosin"[Mesh] OR Xinzhuangtai OR Maipuxin OR Jitai OR Thymo peptide OR Thymo peptides OR Thymopetidium OR Thymostimulin OR Thymopolypeptides OR Thymalfasin OR Thymosin OR Thymosins OR Timunox OR Thymopentin OR Zadaxin). Additionally, we evaluated all systematic reviews and meta-analyses of thymic peptides for MPE, and selected eligible studies from their references.

Study Selection

According to the pre-designed inclusion and exclusion criteria, two reviewers (You-Shu Shen and Yuan-Xiu He) independently collected all eligible studies about intrathoracic infusion therapy of TPs and chemical irritants in MPE. Any disagreements were resolved by discussing themselves or with a third investigator (Zheng Xiao).

Evaluation Of Methodological Bias Risk

According to the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [27], the parameters for methodological bias risk were as follows: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias (e.g., whether the baseline was comparable). Two reviewers (Xiao-Tian Zheng and Ya-Hui Yang) independently evaluated each trial, judged each item as three levels (Yes for a low bias, No for a high risk of bias, and unclear). Any disagreements about judgment of bias risk were solved by discussion between themselves or with a third investigator (Zheng Xiao).

Outcome Measures

The primary outcomes were treatment success, treatment failure, and survival. We integrated previous criteria [28–33] as follows: (1) complete response (CR) is a pleural effusion disappeared for more than four weeks, or the lack of accumulation of fluid; (2) partial response (PR) is a pleural effusion was reduced more than 50% for more than four weeks or a 50% decrease in the effusion; (3) no response (NR) or stable disease (SD) is pleural effusion was reduced less than 50% or increased less than 25% or the effusion recurred but required no further therapy; (4) progressive disease (PD) is pleural effusion increased more than 25% along with other signs of progressive disease or symptomatic re-accumulation of the effusion requiring repeat thoracentesis or chest tube. We defined the treatment success as CR plus PR, and treatment failure as NR/SD plus PD. The survival was evaluated using overall survival (OS) rate, progression-free survival (PFS) rate, or hazard ratio (HR) of the OS and PFS.

Secondary outcomes were QOL, peripheral blood lymphocytes, ADRs, or TRAEs. First, the QOL was considered improved, when the scores increased ten points or higher after treatment according to the Karnofsky Performance Status (KPS) Scale [34–35]. Second, the peripheral blood lymphocytes were represented as the proportions of CD3⁺, CD3⁺ CD4⁺, and CD3⁺ CD8⁺ T cells and ratio of CD4⁺/CD8⁺ T cells, which were detected using flow cytometry or indirect immunofluorescence test after treatment. Third, according to the World Health Organization (WHO) [36] or Common Terminology Criteria for Adverse Events (CTCAE) standards [37], the ADRs were represented as myelosuppression, gastrointestinal toxicity (gastrointestinal reaction and nausea/vomiting), hepatotoxicity (serum aminotransferase or alkaline phosphatase > 1.25 × N), and nephrotoxicity (serum urea nitrogen or creatinine > 1.25 × N), fever, and chest pain. Fourth, the TRAEs were represented as respiratory failure, catheter-related infection/chest infection, pneumothorax, and cutaneous emphysema, among others.

Data Extraction

According to the pre-designed data extraction form, the extracted data were the time of publication; the patient baselines as the primary tumors, volumes of pleural effusion, KPS score, anticipated survival time (AST), IPCs, and treatment process (primary treatment (PT)/retreatment(RT)); cases of experimental and control group; demographic and methodological characteristics; types and usages of TPs and chemical irritants; follow-up protocols; evaluation criteria; and outcomes including treatment success, treatment failure, OS, PFS, QOL, ADRs, TRAEs, and peripheral blood lymphocytes. Two reviewers (Min He and Shu-Guang Li) independently extracted all data. If the studies without Kaplan-Meier survival curves or other relevant data, we contacted their authors to gain available survival data. If the authors unavailable, we re-constructed the Kaplan-Meier survival curves into OS, PFS, and HR using Engauge Digitizer 4.1 [38–39].

Statistical Analysis And Quality Of Evidence

We represented the treatment success, treatment failure, OS rate, PFS rate, QOL, ADRs, TRAEs as odds ratio (OR) and 95% confidence intervals (CI); OS and PFS as HR and 95% CI; and peripheral blood lymphocytes as standardized mean difference (SMD) and 95% CI. We applied the Cochran's χ^2 test and the I^2 statistic to measure potential statistical heterogeneity. $I^2 > 50\%$ meant a statistical heterogeneity. If $p > 0.1$ and $I^2 \leq 50\%$, we summarized the OR, HR, SMD, and their 95% CI using a fixed-effects model. If $I^2 > 50\%$ and without obvious clinical heterogeneity, we summarized the data using a random-effects model. Otherwise, we eliminated the indicator. Two reviewers (Cheng-Qiong Wang and Teng-Yang Fan) performed a series of meta-analyses using Review Manager 5.3 (The Cochrane Collaboration, Oxford, UK). Included studies > 10 , we examined potential publication bias using funnel plot and Egger/Begg's tests. Following our experiences [21, 40–42], if the trial with at least one domain considered as high risk, we defined it as poor quality. In this meta-analysis, and if the result was statistically different and benefit to TPs infusion, we defined the trial as under- or over-estimated trial. Then, we developed a sensitivity analysis model to further examine the results' robustness under extreme conditions as removing the trials with poor quality, under-estimated ADRs, or over-estimated efficacy.

Following previous guidance [43], we developed a subgroup analysis model to examine the heterogeneity and reveal the effects of variables as patient baselines (primary tumors, volume of pleural effusion, KPS score, AST, treatment process, and IPCs), interventions, controls and evaluation criteria on treatment success or treatment failure between different studies. We developed a univariable random effects meta-regression for the relationship between each variable and treatment success or treatment failure, and also a post-hoc multiple regression analysis adjusting for the OR of treatment success and treatment failure under all variables.

Following the Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach [44] and our experiences [21, 40–42], we sorted evidence quality into four grades as high, moderate, low and very low. The criteria of quality degradation were as follows: (1) limitations in study design (trials had unclear risk, and some trials had high risk, if sensitivity analysis was good robust, the evidence was downgraded by one level; if poor, the evidence was downgraded by two levels; all trials had no high risk, and the evidence was downgraded by one level; and if all were poor, the evidence was downgraded by two levels.); (2) statistical heterogeneity (the statistical heterogeneity were shown among the trials, and sensitivity analysis was poor robust); (3) indirectness, (the subjects, interventions, controls, or outcomes did not meet this study); (4) imprecision (the subjects for each outcome < 300); (5) publication bias (the indicator showed a publication bias, and sensitivity analysis was poor robust.). For (2) to (5), the evidence was downgraded by one level. According to the above criteria, two reviewers (Cheng-Qiong Wang and Xiao-Fan Chen) applied GRADE profiler to summarize the evidence quality, and generate absolute estimates of effect for the treatment success, treatment failure, OS, PFS, QOL, ADRs, TRAEs, and peripheral blood lymphocytes.

Results

Search Results

This meta-analysis collected 357 records using search strategies (Fig. 1). First, we read the title and collected 164 records. Second, we further read the abstract, and collected 120 full-texts and one meta-analysis [22]. Third, we evaluated the full-text and collected 24 eligible trials [23–25, 45–65]. We evaluated the meta-analysis [22], and collected six eligible trials [56–57, 59–60, 62, 64] from its references. Finally, deleting the duplicates, we included 24 eligible trials [23–25, 45–65] for this meta-analysis.

Characteristics Of Included Trials

This meta-analysis collected 24 eligible trials [23–25, 45–65] with 1,592 patients and three TPs and platinum for analysis (Table 1). Patient ages ranged from 27 to 78 years old, and 911 and 627 cases were male and female, respectively. The experimental group was administered TPs with platinum in 798 cases, and the control group was administered platinum alone in 794 cases. Seventeen trials described 1214 patients with lung cancer [23–25, 48, 50–51, 53, 56–65]; seven trials described 378 patients with lung, breast, or ovarian cancer, among others [45–47, 49, 52, 54–55]; 15 trials with 1021 patients [46–52, 54–57, 59, 61–62, 64] had moderate to large volume of pleural effusion; 23 trials [23–25, 45–65] described the IPCs; some trials did described the patient baselines as KPS score and AST; and no trials described the treatment process. The TPs were used with thymosin (200–300 mg/time), thymopentin (2 mg/time) or T α 1 (3.2 mg/time), and the platinum were DDP (30–40 mg/m²), carboplatin (CBP) (400 mg/m²), and oxaliplatin (L-OHP) (100 mg/m²). The TPs and platinum were used with one to two times per week for one to eight times. The indicators were measured after treatment four to 12 months. Twenty-four trials with 1,592 patients [23–25, 45–65] all reported the treatment success and failure, and two trials with 226 patients [57, 62] reported the OS rate. Seven trials with 374 patients [45–46, 49, 54–56, 60] reported the QOL; 19 trials with 1,266 patients [25, 45–51, 53–58, 60–63, 65] reported the ADRs; two trials with 136 patients [47, 51] reported the TRAEs; and 10 trials with 848 patients [23–25, 55–57, 59, 61–62, 64] reported the peripheral blood lymphocytes using flow cytometry.

Methodological Bias Risk

Of the 24 trials, 10 trials reported random sequence generation using a random number table [24, 48, 53, 55, 61] or coin toss [49, 57, 65], draw [64], or computer random [23]. None of trials described the concealment and blinding. All trials had complete outcome data. Ten trials failed in completely reporting the ADRs or TRAEs [45–51, 53, 56, 63]. Except for the one trial [45], others' baseline had comparability. The risk of methodological bias was shown in Fig. 2.

Clinical Response

Twenty-four trials [23–25, 45–65] with 1,592 patients reported the treatment success/ failure (Fig. 3a and 3b). Cochran's χ^2 test and I^2 statistic did not find statistical heterogeneity in treatment success and failure ($I^2 = 0\%$). Therefore, the data of treatment success and failure was summarized by using a fixed-effects model. Compared with platinum alone, the result of meta-analysis demonstrated that intrathoracic infusion of TPs with platinum significantly improved the treatment success [OR = 4.02, 95% CI (3.12 to 5.18), $p < 0.00001$] and decreased the treatment failure [OR = 0.25, 95% CI (0.19 to 0.32), $p < 0.00001$].

Quality Of Life

According to the KPS scale, seven trials [45–46, 49, 54–56, 60] with 374 patients reported QOL (Fig. 3c). Cochran's χ^2 test and I^2 statistic did not find statistical heterogeneity in QOL ($I^2 = 0\%$). The data of QOL was summarized by using a fixed-effects model. Compared with platinum alone, the result demonstrated that TPs with platinum significantly improved the QOL [OR = 3.64 95% CI (2.34 to 5.66), $p < 0.00001$].

Overall Survival

Two trials with 226 patients [57, 62] reported the OS rates (Fig. 4). There was no heterogeneity in 0.5- or 1-year OS rates ($I^2 = 0\%$). Therefore, the data of OS rate was summarized by using a fixed-effects model. The results demonstrated that TPs with platinum significantly increased the 0.5- and 1-year OS rate [OR = 5.75, 95% CI (3.02 to 10.92), $p < 0.00001$, and OR = 5.29, 95% CI (1.71 to 16.36), $p = 0.004$].

Peripheral Blood Lymphocytes

Nine trials with 790 patients [23, 25, 55–57, 59, 61–62, 64] reported the peripheral blood lymphocytes (Fig. 5). Cochran's χ^2 test and I^2 statistic found statistical heterogeneity in CD3⁺ T cells ($I^2 = 91\%$), CD3⁺ CD4⁺ T cells ($I^2 = 93\%$), CD3⁺ CD8⁺ T cells ($I^2 = 96\%$), and CD4⁺/CD8⁺ T cell ratio ($I^2 = 67\%$). Three trials [25, 57, 61] reported that TPs with platinum significantly increased the proportions of CD3⁺ CD8⁺ T cells, and one trial [23] reported that it significantly decreased the CD3⁺ CD8⁺ T cells. Then, the result had a significant clinical heterogeneity. Therefore, we only summarized the data on CD3⁺ T cells, CD3⁺ CD4⁺ T cells, and CD4⁺/CD8⁺ T cells ratio using a random-effects model. The results demonstrated that TPs with platinum significantly increased the proportions of CD3⁺ T cells [SMD = 1.10, 95% CI (0.54 to 1.66), $p = 0.0001$], CD3⁺ CD4⁺ T cells [SMD = 1.93, 95% CI (1.29 to 2.57), $p < 0.00001$], as well as the ratio of CD4⁺/CD8⁺ T cells [SMD = 0.70, 95% CI (0.36 to 1.04), $p < 0.0001$].

Adverse Drug Reactions And Thoracentesis-related Adverse Events

Nineteen trials containing 1,266 patients [25, 45–51, 53–58, 60–63, 65] reported the ADRs, and two trials [47, 51] reported the TRAEs (Table.2 and Fig.S1-S7). Cochran's χ^2 test and I^2 statistic found minimal heterogeneity in myelosuppression ($I^2 = 14\%$), and no heterogeneity in other ADRs or TRAE ($I^2 = 0\%$). Therefore, the data of ADRs and TRAEs was summarized by using a fixed-effects model. The results demonstrated that TPs with platinum resulted in a lower incidence rate of myelosuppression [OR = 0.46, 95% CI (0.31 to 0.69), $p = 0.0001$], gastrointestinal toxicity [OR = 0.46, 95% CI (0.33 to 0.64), $p < 0.00001$] than platinum alone. However, no statistical differences were shown in chest pain, fever, hepatotoxicity, and nephrotoxicity. Additionally, two trials with 136 patients [47, 51] reported that no TRAEs had occurred in both groups.

Subgroups And Meta-regression Analysis

Patient baselines were the primary tumors, volume of pleural effusion, KPS score, and AST. First, primary tumors included malignant tumors and lung cancer. The results of subgroup analysis demonstrated that intrathoracic infusion of TPs with platinum significantly improved the treatment success, and resulted in a low risk of failure for MPE from lung cancer and malignant tumors (Table.3a, Fig.S8 and S10). According to volume of pleural effusion, MPE was mainly moderate to large. TPs with chemical platinum significantly improved the treatment success, resulted in a low risk of failure (Table.3b, Fig.S12 and S14). KPS scores were ≥ 50 , and ≥ 60 , and AST was mainly ≥ 3 months. Intrathoracic infusion of TPs also achieved the above effects in patients with KPS scores ≥ 50 or ≥ 60 (Table.3c, Fig.S16 and S18), or AST ≥ 3 months (Table.3d, Fig.S20 and S20). Univariable meta-regression did not find any correlation between treatment success / failure and any of baselines ($p = 0.93$ for primary tumor, $p = 0.67$ for volume of pleural effusion, $p = 0.71$ for KPS, and $p = 0.70$ for AST) (Table.3 and Fig.S9, S11, S13, S15, S17, S19, S21, and S23).

The TPs were used with thymosin (200–300 mg/time), thymopentin (2 mg/time) or Ta1 (3.2 mg/time), and the platinum were DDP (30–40 mg/m²), CBP (400 mg/m²), and L-OHP (100 mg/m²). The subgroup analysis demonstrated that intrathoracic infusion of thymosin, thymopentin or thymalfasin with DDP, CBP, or L-OHP all significantly improved the treatment success, and resulted in a low risk of failure (Table.3e and 3f, Fig.S24, S26, S 28, and S30). The TPs with platinum was used with once or twice a week, and it achieved the above effects (Table.3 g, Fig.S32 and S34). Treatment lasting one to eight times, mainly three to four times, it still did so (Table.3 h, Fig.S36 and 38). The evaluation criteria were Millar and Ostrowskimj [28–33]. The TPs with platinum achieved the above effects using the two criteria (Table.3i, Fig.S40 and 42). Univariable meta-regression showed no correlation between treatment success/failure and variables ($p = 0.99$ for TPs, $p = 0.85$ for platinum, $p = 0.96$ for treatment frequency, and $p = 0.73$ for treatment times, and $p = 0.93$ for criteria) (Table.3 and Fig.S25, S27, S29, S31, S33, S35, S37, S39, S41 and S43). Finally, multiple meta-regression analysis did not find any correlation between treatment success/failure and all variables (Table 3).

Publication Bias Analysis

According to the funnel plots and Egger/Begg's tests, no publication bias was found in trials for treatment success ($p = 0.26$, 95% CI - 0.41 to 1.43), treatment failure ($p = 0.26$, 95% CI - 1.43 to 0.41), myelosuppression ($p = 0.08$, 95% CI - 3.63 to 0.22), and gastrointestinal toxicity ($p = 0.13$, 95% CI - 2.14 to 0.30), all outcomes were objectively reported (Fig. 6a–6d).

Sensitivity Analysis

In this meta-analysis, 10 trials with poor quality [45–51, 53, 56, 63] were shown in treatment success, treatment failure, QOL, myelosuppression, gastrointestinal toxicity, fever, TRAEs, CD3⁺ T cells, CD3⁺ CD4⁺ T cells, and CD4⁺/CD8⁺ T cells ratio. The results of sensitivity analysis demonstrated that all results were robust before and after rejecting the poor trials (Table 4a-4b). The trials might over-estimate the treatment success, QOL, 0.5-year OS rate, 1-year OS rate, CD3⁺ T cells, CD3⁺ CD4⁺ T cells, and CD4⁺/CD8⁺ T cells ratio, and under-estimate the treatment failure, myelosuppression, and gastrointestinal toxicity. The results of sensitivity analysis demonstrated that except for the 0.5-year and 1-year OS rate, other results had robustness before and after rejecting the trials with over-estimated efficacy or under-estimated ADRs (Table 4c-4d). In all, most results were robust.

Quality Of Evidence

In methodology, 10 poor trials [45–51, 53, 56, 63] were shown in treatment success, treatment failure, QOL, myelosuppression, gastrointestinal toxicity, fever, TRAEs, CD3⁺ T cells, CD3⁺ CD4⁺ T cells, and CD4⁺/CD8⁺ T cells ratio, and all results were robust; therefore, we downgraded their quality with one level. Statistical heterogeneity was shown in CD3⁺ T cells, CD3⁺ CD4⁺ T cells, and CD4⁺/CD8⁺ T cells ratio, and sensitivity analysis showed good robustness; and no publication bias was shown in treatment success, treatment failure, myelosuppression, and gastrointestinal reaction; therefore, we did not downgrade their quality. The sample size for 0.5-year, one-year OS rate, hepatotoxicity, nephrotoxicity, and TRAEs were less than 300 patients, therefore, we downgraded their quality with one level. No outcomes were eligible for upgrade. Taken together, the quality of evidence was very low for TRAEs; low for 0.5-year, one-year OS rate, hepatotoxicity, nephrotoxicity; and moderate for others (Table.5).

Discussion

With the exception of adjuvant therapy for malignant tumors, intrathoracic infusion of TPs with chemical irritants is also used in the control of MPE. In this meta-analysis, we included 24 eligible trials [23–25, 45–65] with 1,592 patients to determine whether they improve the clinical efficacy and survivals. Compared with platinum alone, the results of meta-analysis demonstrated that TPs in combination with platinum significantly improved the treatment success, QOL, 0.5-year and 1-year OS rate, and reduced the incidence of treatment failure, myelosuppression, and gastrointestinal toxicity in MPE. Most trials only reported ADR, and ignored potential TRAEs. In addition, they significantly increased the proportions of CD3⁺ T cells, CD3⁺ CD4⁺ T cells, and the ratio of CD4⁺/CD8⁺ T cells. In methodology, most had unclear bias risk, and 10 poor [45–51, 53, 56, 63] failed in completely reporting the ADRs. The peripheral blood lymphocytes had statistical heterogeneity, the CD3⁺ CD8⁺ T cells had obvious clinical heterogeneity, and we summarized the data using a random-effects model. As a result of limited trials, we gave up exploring the reason of heterogeneity using subgroup analysis. The trials objectively reported the treatment success, failure, myelosuppression, and gastrointestinal toxicity. The 0.5-year and 1-year OS rate were poor robust. With the exception of the anemia, thrombocytopenia, TRAEs, 0.5-year, one-year OS rate, hepatorenal toxicity, all outcomes had moderate quality based on the GRADE approach.

A meta-analysis [22] reported that thymosin combined with oxaliplatin might improve the clinical response, and host immunity, and with low incidences of the ADRs in lung cancer patient with MPE. However, the meta-analysis [22] had many shortcomings in the methodology, and an increasing new clinical trials have reported on the evaluation of TPs with platinum. This meta-analysis improved the design, integrated previous meta-analysis [22], and supplemented 18 trials with 1,132 patients [23–25, 45–55, 58, 61, 63, 65], and further demonstrated that intrathoracic infusion of TPs with platinum significantly improved the treatment success, 0.5-year, one-year OS rate, and with low incidences of the treatment failure, myelosuppression and gastrointestinal toxicity. In addition, we found that they significantly up-regulated the level of peripheral blood lymphocytes. Our related systematic review and meta-analysis [21] found that the sTP, especially Ta1 with chemotherapy might improve the anti-tumor immunity, tumor response, QOL and 1- year OS rate of lung cancer. Another related study [66] reported that the thoracic injection of low-dose interleukin-2 significantly improved the clinical response and QOL of patients with MPE. Oka M, et.al [67] reported that an important BRM, Lentinan significantly improved clinical response and augmented lymphokine activated killer activity through intrathoracic infusion for patients with malignant peritoneal and/or pleural effusions. These results provided the indirect evidence of our findings. Based on this meta-analysis findings and evidence quality, we believe that intrathoracic infusion of TPs with platinum may improve the treatment success, QOL, 0.5-year, one-year OS rate, up-regulate the level of peripheral blood lymphocytes, and with low incidences of the treatment failure, myelosuppression and gastrointestinal toxicity. But, these results may under-estimate the ADRs and TRAEs (Fig. 7).

In 24 trials, patient baselines, types and usages of TPs and platinum had marked diversity. Hence, we carried out a series of subgroup analyses to reveal the optimal condition of TPs with platinum. The subgroup analysis found that the TPs with platinum all significantly improved the treatment success, and with a low risk of failure in patients with moderate to large volume of pleural effusion, KPS scores ≥ 50 or ≥ 60 , or AST ≥ 3 months. Chemical pleurodesis is considered by many as a first-line intervention in MPE without a NEL, particularly in cases with an AST of > 3 months [68–69]. Additionally, Yoon DW et al [70] reported that the KPS score (≥ 50 to 60) was independent predictor of a poor survival after video-assisted thoracoscopic surgery (VATS)-mediated talc pleurodesis. Compared with VATS-mediated talc pleurodesis, the TPs with platinum seems to have a lower threshold. These findings indicate that moderate to large volume of pleural effusion, KPS score ≥ 50 to 60, or AST ≥ 3 months may be the therapeutic threshold for TPs with platinum infusion. Millar or Ostrowskimj criteria and the type of primary tumor had no negative impact on these results. Whether it also does for primary treatment/retreatment or drug-

resistant patients remain unclear. The subgroup analysis further found that intrathoracic infusion of thymosin (200–300 mg/time), thymopentin (2 mg/time) or Ta1 (3.2 mg/time) with DDP (30–40 mg/m²), CBP (400 mg/m²), or L-OHP (100 mg/m²), all significantly improved the treatment success, and with a low risk of failure. The TPs with platinum was used once or twice a week, mainly for 3–4 times. Interestingly, the thymosin, thymopentin or thymalfasin in combination with DDP, CBP, or oxaliplatin all significantly improved the treatment success, with a low risk of failure. However, univariable and post-hoc multiple regression analysis did not find any positive correlation, and these conclusions from the subgroup analysis belonged to indirect evidence. As a result of limited trials, this meta-analysis didn't demonstrate the optimal TPs type, usage and combination with platinum for achieving the best response, and the relationship between TPs and platinum also needs to be confirmed by new trials.

Based on the optimization of success and failure, we believe that the moderate to large volume of pleural effusion, KPS score ≥ 50 to 60, or AST ≥ 3 months may be the therapeutic threshold for TPs with platinum infusion. The thymosin (200–300 mg/time), thymopentin (2 mg/time) or Ta1 (3.2 mg/time) with DDP (30–40 mg/m²), CBP (400 mg/m²), or L-OHP (100 mg/m²) are possible regimens for producing a desired treatment success, and low failure. The optimal type, usage and combination with platinum for achieving the best response need to be confirmed by new trials. If successful, these findings will be important for defining therapeutic threshold, developing rational usage of TPs and platinum, and attaining an individualized TPs intrathoracic infusion therapy for MPE (Fig. 7).

There were some shortcomings in this meta-analysis. First, we only retrieved Chinese and English databases, which might have led to retrieval bias. Second, most trials did not describe the volume of pleural effusion, KPS score, AST, and treatment process. Third, only ten trials [23–24, 48–49, 53, 55, 57, 61, 64–65] described random sequence generation, and ten trials [45–51, 53, 56, 63] failed in completely reporting the ADRs, and most ignored potential TRAE and PFS. Fourth, their quality was moderate to very low. Univariable and multiple meta-regression analysis did not find any positive correlation. Fifth, there was lack of a unified standard for clinical response. As a result of limited trials, this meta-analysis didn't demonstrate the optimal type, usage and combination with platinum for achieving the best response. All of these shortcomings might have led to insufficient evaluation of the outcomes.

Conclusions

The evidence indicates that intrathoracic infusion of TPs with platinum may improve the treatment success, QOL, 0.5-year, and one-year OS rate, up-regulate the level of peripheral blood lymphocytes, and with low incidences of the treatment failure, myelosuppression and gastrointestinal toxicity. The moderate to large volume of pleural effusion, KPS score ≥ 50 to 60, or AST ≥ 3 months may be the therapeutic threshold for TPs with platinum infusion. The thymosin (200–300 mg/time), thymopentin (2 mg/time) or Ta1 (3.2 mg/time) with DDP (30–40 mg/m²), CBP (400 mg/m²), or L-OHP (100 mg/m²) are possible regimens for producing a desired treatment success, and low failure. The optimal type, usage and combination with platinum for achieving the best response remain unclear. Additionally, whether TPs with platinum improve the OS and PFS, also do for retreatment or drug-resistant patients; the dosage relationship between TPs and platinum; and their ADRs and potential TRAE needs to be determined further.

Appendix

Supplementary material.1 Retrieval results; Supplementary material.2 Meta-analysis results of ADRs (Fig.S1-7); Supplementary material.3 Subgroup analysis results (Fig.S8-43); Supplementary material.4 PRISMA Checklist

Abbreviations

ADRs: Adverse drug reactions; AST: Anticipated survival time; BRMs: Biological response modifiers; CBM: China Biological Medicine Database; CBP: Carboplatin; CENTRAL: Cochrane Central Register of Controlled Trials; CI: Confidence intervals; CNKI: China National Knowledge Infrastructure Database; CR: Complete response; CTCAE: Common Terminology Criteria for Adverse Events; DDP: Cisplatin; GRADE approach: Grades of Recommendation Assessment, Development and Evaluation approach; HR: Hazard ratio; IPCs: Indwelling pleural catheters; KPS: Karnofsky Performance Status; L-OHP: Oxaliplatin; MPE: Malignant pleural effusion; NEL: Nonexpendable lung; NR: No response; NSCLC: Non-small cell lung cancer; OR: Odds ratio; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; PRISMA guidelines: Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines; pTE: Purified thymus extracts; QOL: Quality of life; RCTs: Randomized controlled trials; SD: Stable disease; SMD: Standardized mean difference; SM: Statistical method; sTP: Synthetic thymic peptides; Ta1: Thymosin alpha 1; TCM: Traditional Chinese medicine; TPs: Thymic peptides; TRAEs, Thoracentesis-related adverse events; VATS: Video-assisted thoracoscopic surgery; VIP: Chinese Scientific Journals Full-Text Database; WHO: World Health Organization.

Declarations

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Authors' Contributions

Conception and design by Zheng Xiao, Xue Xiao, and Xiao-Fan Chen; development of methodology by Zheng Xiao, Cheng-Qiong Wang, and Xiao-Fan Chen; literature search by Cheng-Qiong Wang and Min He; article selection by You-Shu Shen and Yuan-Xiu He; assessment of methodological bias risk by Xiao-Tian Zheng and Ya-Hui Yang; data extraction by Min He and Shu-Guang Li; statistical analysis by (Cheng-Qiong Wang and Teng-Yang Fan); GRADE assessment by Cheng-Qiong Wang and Xiao-Fan Chen; preparing the manuscript draft by Zheng Xiao and Xue Xiao; review and revision of the manuscript by Xue Xiao, Xiao-

Fan Chen, Ji-Hong Feng, Xing-sheng Yao; and study supervision by Zheng Xiao and Xue Xiao. All authors read and approved the final version of the manuscript.

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Availability of data and materials

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

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table.1 Characteristics of included trials											
First author, Year	Malignant pleural effusion								Interventions		ET
	PTs	Volume	KPS	AST	IPC	E/C	M/F	Years	Thymic peptides	Chemical irritants	
Zhao, M.2002[45]	Un	Unclear	>40	Un	No	23/22	32/13	34-73	Thymosin:60mg, 1time/w, 1-4times	CBP:400mg/m ²	4w
Li, F.2004[46]	Un	Large	≥50	Un	Yes	21/20	30/11	53-75	Thymosin:120mg, 1time/5-7d, 1-3times	DDP:60-80mg/m ²	Un
Lin, B.2005[47]	MTs	Moderate to large	Un	Un	Yes	30/30	26/34	27-69	Thymopentin:10mg, 1time/2d, 1-2times	DDP:80mg/m ²	6-12m
Gao, Y.2010[48]	LC	Moderate	>60	Un	Yes	21/21	29/13	36-75	Thymopentin:2mg, 1time/w, 4times	CBP:400mg/m ²	5w
Guo, C.2011[49]	MTs	Moderate to large	≥60	>3m	Yes	19/18	21/16	37-76	Thymlfasin:3.2mg, 1time/w, 3times	DDP:40mg/m ²	4w
He, R.2011[50]	LC	Moderate	>60	Un	Yes	25/25	36/14	37-72(59.5)	Thymopentin:2mg, 1time/w, 4times	CBP:400mg/m ²	4w
Mo, Z.2012[51]	LC	Moderate to large	Un	Un	Yes	38/38	37/39	32-71	Thymopentin:10mg, 1time/2d, 1-2times	DDP:80mg/m ²	4w
Wu, Z. 2012[52]	MTs	Moderate to large	>50	Un	Yes	26/26	36/16	48-78	Thymosin:300mg, 2times/w, Unclear	DDP:40mg/m ²	Un
Zhang, X.2012[53]	LC	Unclear	>60	Un	Yes	27/27	Un	41-78	Thymopentin:2mg, 1time/w, 4times	DDP:80mg/m ²	5w
Tan, J.2013[54]	MTs	Large	Un	Un	Yes	24/23	28/19	31-68	Thymosin:300mg, Unclear	DDP:50-60mg/m ²	4w
Huo, W.2014[55]	MTs	Moderate to large	≥70	>3m	Yes	48/48	46/50	33-74	Thymlfasin:3.2mg, 1time/w, 4times	DDP:40mg/m ²	4w
Liang, X.2015[56]	LC	Moderate to large	≥60	>3m	Yes	24/24	29/19	35-66	Thymosin:300mg, 1time/w, 2times	L-OHP:100mg/m ²	4w
Yang, M.2016[57]	LC	Moderate to large	≥50	>3m	Yes	60/60	74/46	51.05±12.5; 50.28±10.9	Thymosin:300mg, 1time/w, 8times	L-OHP:100mg/m ²	6-12m
Su, C.2017[58]	LC	Small	Un	Un	Yes	34/34	28/40	36-78(54.4)	Thymosin:200mg, 1time/4d, 4times	DDP 20mg/m ²	16d
Ying, Y.2017[59]	LC	Moderate to large	>60	>3m	Yes	18/18	21/15	51+12	Thymosin:300mg, 1time/w, 2times	L-OHP:100mg/m ²	1m
Zhou, Z.2017[60]	LC	Unclear	Un	>3m	Yes	30/30	29/31	33-66	Thymosin:300mg, 1time/w, 4times	L-OHP:100mg/m ²	4w
Chen, X. 2018[61]	LC	Moderate to large	Un	Un	Yes	60/60	88/32	40-74	Thymosin:300mg, 1time/3w, 3-4times	L-OHP:100mg/m ²	9-12w
Liu, T.2018[62]	LC	Moderate to large	≥50	>3m	Yes	53/53	65/41	Unclear	Thymosin:300mg, 1time/w, 4times	L-OHP:100mg/m ²	8w
Lu, S. 2018[63]	LC	Unclear	≥50	>3m	Yes	30/30	31/29	34-78	Thymosin:300mg, Unclear	L-OHP:100mg/m ²	Un
Wang, Z.2018[64]	LC	Moderate to large	Un	Un	Yes	45/45	56/34	33-67	Thymosin:300mg, 1ime/w, 8times	L-OHP:100mg/m ²	8w
Yu, G. 2018[65]	LC	Unclear	Un	Un	Yes	26/26	31/21	36-68	Thymosin:300mg, 1time/w, 4times	L-OHP:100mg/m ²	4w
Zhao, J.2018[23]	LC	Unclear	Un	Un	Yes	35/35	42/28	42-78	Thymosin:300mg, 1time/w, 2times	L-OHP:30mg/m ²	Un
Chen, C.2019[24]	LC	Unclear	Un	>3m	Yes	39/39	45/33	50.2±4.6; 51.6±4.1	Thymosin:300mg, 1time/w, 8times	L-OHP:100mg/m ²	8w
Luo, Z.2019[25]	LC	Unclear	Un	Un	Yes	42/42	51/33	36-78	Thymosin:300mg, 1time/w, 8times	L-OHP:100mg/m ²	8w

NOTE: PTs: primary tumors, MTs: malignant tumors, LC: lung cancer, KPS score: Karnofsky Performance Status score, AST: anticipated survival time, IPCs: in TPs: thymic peptides, E/C: experimental group (TPs with chemical irritants)/control group (chemical irritants alone), F/M: female/male, DDP: cisplatin, CBP: carboplatin, ET: Evaluation time. Milla: complete response, partial response, stable disease and progressive disease (PD); Ostrowskimj: CR, PR, and no response (NR). WH for adverse drug reactions. Outcome: O1: treatment success/failure, O2: Quality of life (QOL), O3: survival, O4: adverse drug reactions (ADRs) and thoracentesis (TRAEs), and O5: peripheral blood lymphocytes; Un Unclear.

Table 2. Meta-analysis results of ADRs and TRAEs (Fig.S1-7)

Outcomes	Trials	Experimental group (Evens/total)	Control groups (Evens/total)	SM	Effect Estimate (OR, 95% CI)	I^2	p
Myelosuppression (Fig.S1)	14	46/504	86/503	FEM	0.46 [0.31, 0.69]	14%	$p=0.0001$
Gastrointestinal toxicity (Fig.S2)	17	84/589	142/587	FEM	0.46 [0.33, 0.64]	0%	$p<0.00001$
Chest pain (Fig.S3)	6	13/302	20/302	FEM	0.63 [0.31, 1.30]	0%	$p=0.21$
Fever (Fig.S4)	8	48/315	51/315	FEM	0.92 [0.59, 1.45]	0%	$p=0.73$
Hepatotoxicity (Fig.S5)	3	4/100	6/91	FEM	0.51 [0.14, 1.96]	0%	$p=0.33$
Nephrotoxicity (Fig.S6)	2	2/108	3/108	FEM	0.66 [0.11, 4.07]	No	$p=0.65$
TRAEs (Fig.S7)	2	0/68	0/68	No	No	No	No
Note: ADRs: adverse drug reactions, TRAEs: thoracentesis-related adverse events, SM: statistical method, FEM: fixed-effects model, OR: odds ratio.							

Table.3 Subgroups and meta-regression analysis									
Subgroups	Assign	Trials	Cases	Treatment success			Treatment failure		
				OR(95%CI)	UM	MM	OR(95%CI)	UM	MM
Table.3a Subgroups analysis via primary tumors (Fig.S8–11)									
Malignant tumors	1	7	378	3.94[2.45,6.34]	0.93	0.71	0.25[0.16,0.41]	0.93	0.71
Lung cancer	2	17	1214	4.05[3.00,5.46]			0.25[0.19,0.32]		
Table.3b Subgroups analysis via volume of pleural effusion (Fig.s12–15)									
Moderate to large	2	15	1021	3.86[2.84,5.25]	0.67	0.96	0.26[0.19,0.35]	0.67	0.96
Others	1	9	571	4.36[2.80,6.79]			0.23[0.15,0.36]		
Table.3c Subgroups analysis via KPS score (Fig.S16–19)									
KPS score (≥50)	2	5	379	4.05[2.42,6.81]	0.71	0.66	0.25[0.15,0.41]	0.71	0.66
KPS score (≥60)	3	7	363	3.70[2.26,6.05]			0.27[0.17,0.44]		
Unclear	1	12	850	4.18[2.92,5.99]			0.24[0.17,0.34]		
Table.3d Subgroups analysis via anticipated survival time (AST) (Fig.S20–23)									
AST (≥3 months)	2	9	941	3.80[2.58,5.58]	0.70	0.99	0.26[0.18,0.39]	0.70	0.99
AST (Unclear)	1	15	951	4.20[3.00,5.87]			0.24[0.17,0.33]		
Table.3e Subgroups analysis via different thymic peptides (Fig.S24–27)									
Thymosin (200 to 300mg/time)	1	17	1177	3.97[2.93,5.38]	0.99	0.67	0.25[0.19,0.34]	0.99	0.67
Thymopentin (2mg/time)	2	5	282	4.38[2.49,7.69]			0.23[0.13,0.40]		
Thymosin alpha1 (3.2mg/time)	3	2	133	3.69[1.66,8.19]			0.27[0.12,0.60]		
Table.3f.Subgroups analysis via different platinum (Fig.S28–31)									
Oxaliplatin	1	12	924	3.96[2.79,5.63]	0.85	0.99	0.25[0.18,0.36]	0.85	0.99
Cisplatin	2	9	531	4.02[2.68,6.03]			0.25[0.17,0.37]		
Carboplatin	3	3	137	4.38[1.92,9.97]			0.23[0.10,0.52]		
Table.3g Subgroups analysis via treatment frequency(Fig.S32–35)									
One time/week	2	17	1109	3.99[2.94,5.40]	0.96	0.73	0.25[0.19,0.34]	0.96	0.73
Two times/week	3	2	120	4.10[1.70,9.89]			0.24[0.10,0.59]		
Others	1	5	363	4.10[2.39,7.03]			0.24[0.14,0.42]		
Table.3h Subgroups analysis via treatment times (Fig.S36–39)									
One to two times	2	5	290	4.24[2.40,7.52]	0.73	0.65	0.24[0.13,0.42]	0.73	0.65
Three to four times	3	10	683	4.06[2.76,5.97]			0.25[0.17,0.36]		
Eight times	4	4	372	3.64[2.09,6.35]			0.27[0.16,0.48]		
Others	1	5	247	4.17[2.25,7.74]			0.24[0.13,0.45]		
Table.3i Subgroups analysis via different criteria (Fig.S40–43)									
Millar*	1	12	857	3.98[2.81,5.64]	0.93	0.92	0.25[0.18,0.36]	0.93	0.92
Ostrowskimj*	2	12	735	4.06[2.81,5.87]			0.25[0.17,0.36]		
Note: KPS score: Karnofsky Performance Status score, Others: unclear or ungroupable, AST: predicted survival time, OR: odds ratio; CI: confidence interval; UM*: univariable meta-regression, MM*: multiple meta-regression.									

Table.4 Sensitivity analysis										
Indicators	Trials	SM	OR(95%CI)	ι^2	Excluded trials	Trials	SM	OR(95%CI)	ι^2	
Table.4a Sensitivity analysis by excluding the poor studies										
Treatment success	24	FEM	4.02 [3.12, 5.18]	0%	Poor* [45-51, 53, 56, 63]	14	FEM	3.85 [2.81, 5.29]	0%	
Treatment failure	24	FEM	0.25 [0.19, 0.32]	0%	Poor* [45-51, 53, 56, 63]	14	FEM	0.26 [0.19, 0.36]	0%	
Quality of life (QOL)	7	FEM	3.64 [2.34, 5.66]	0%	Poor*[45-46, 49, 56]	3	FEM	2.81 [1.56, 5.03]	0%	
Myelosuppression	14	FEM	0.46 [0.31, 0.69]	14%	Poor*[48-50, 53, 56, 63]	8	FEM	0.35 [0.20, 0.60]	21%	
Gastrointestinal toxicity	17	FEM	0.46 [0.33, 0.64]	0%	Poor*[46-50, 53, 56, 63]	9	FEM	0.43 [0.28, 0.67]	0%	
Fever	8	FEM	0.91 [0.76, 1.09]	0%	Poor*[48, 50, 53]	5	FEM	0.70 [0.39, 1.26]	0%	
TRAEs	2	No	No	No	No	No	No	No	No	
Table.4b Sensitivity analysis excluding the under- or over-estimated studies										
Treatment success	24	FEM	4.02 [3.12, 5.18]	0%	Over*[23, 45-48, 51-53, 55, 57-58, 60-65]	7	FEM	3.21 [1.94, 5.31]	0%	
Treatment failure	24	FEM	0.25 [0.19, 0.32]	0%	Over*[23, 45-48, 51-53, 55, 57-58, 60-65]	7	FEM	0.31 [0.19, 0.52]	0%	
Quality of life (QOL)	7	FEM	3.64 [2.34, 5.66]	0%	Over*[45-46, 49, 55-56]	2	FEM	2.91 [1.30, 6.50]	0%	
0.5-year OS rate	2	FEM	5.75 [3.02, 10.92]	0%	Over* [57, 62]	No	No	No	No	
1-year OS rate	2	FEM	5.29 [1.71, 16.36]	0%	Over* [57, 62]	No	No	No	No	
Myelosuppression	14	FEM	0.46 [0.31, 0.69]	14%	Under*[57, 62]	12	FEM	0.60 [0.39, 0.92]	0%	
Gastrointestinal toxicity	17	FEM	0.46 [0.33, 0.64]	0%	Under*[47, 56-57, 62]	13	FEM	0.61 [0.41, 0.90]	0%	
Peripheral blood lymphocytes	Trials	SM	SMD (95% CI)	ι^2	Excluded trials (Reference number)	Trials	SM	SMD (95% CI)	ι^2	
Table 4c. Sensitivity analysis by excluding the poor trials										
CD3 ⁺ T cells	8	REM	1.10 [0.54, 1.66]	91%	Over* [56]	7	REM	1.03 [0.42, 1.64]	92%	
CD3 ⁺ CD4 ⁺ T cells	9	REM	1.93 [1.29, 2.57]	93%	Over* [56]	8	REM	1.97 [1.26, 2.68]	94%	
CD4 ⁺ /CD8 ⁺ T cells ratio	6	REM	0.70 [0.36, 1.04]	67%	Over* [56]	6	REM	0.76 [0.38, 1.14]	70%	
Table 4d. Sensitivity analysis by excluding the over- or under-estimated trials										
CD3 ⁺ T cells	8	REM	1.10 [0.54, 1.66]	91%	Over* [56-57, 59, 62]; Under* [55, 61]	2	FEM	1.33 [0.98, 1.68]	0%	
CD3 ⁺ CD4 ⁺ T cells	9	REM	1.93 [1.29, 2.57]	93%	Over*[25, 56-57, 59, 61-62, 64]	2	FEM	1.04 [0.73, 1.35]	0%	
CD4 ⁺ /CD8 ⁺ T cells ratio	6	REM	0.70 [0.36, 1.04]	67%	Over* [55, 62, 64]	3	FEM	0.42 [0.12, 0.73]	0%	
Note: Thoracentesis-related adverse events (TRAEs), TNF- α : tumor necrosis factor-alpha, SM: statistical method, FEM: fixed-effects model, REM: random-effects model, OR: odds ratio, SMD: standardized mean difference, CI: confidence interval; Poor trials (Poor*) had at least one domain considered as high risk of bias; Over* or Under*: over or underestimated trials which results were significant difference and beneficial to TPs perfusion.										

Table.5 GRADE evidence profile of clinical efficacy and safety										
Outcomes (Trials)	Quality assessment					MPE		Clinical efficacy and safety		Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	TPs	Platinum	Odds ratios (95% CI)	Absolute effect	
Treatment success (24)	Serious ^a	No	No	No	None	690/798 (86.5%)	495/794 (62.3%)	4.02 (3.12 to 5.18)	246 more per 1000 (from 214 more to 272 more)	ÅÅÅÅ
Treatment failure (24)	Serious ^a	No	No	No	None	108/798 (13.5%)	299/794 (37.7%)	0.25 (0.19 to 0.32)	245 fewer per 1000 (from 215 fewer to 274 fewer)	ÅÅÅÅ
Quality of life (7)	Serious ^a	No	No	No	None	143/189 (75.7%)	85/185 (45.9%)	3.64 (2.34 to 5.66)	296 more per 1000 (from 206 more to 368 more)	ÅÅÅÅ
0.5-year OS rate (2)	Serious ^b	No	No	Serious ^c	None	95/113 (84.1%)	56/113 (49.6%)	5.75 (3.02 to 10.92)	354 more per 1000 (from 252 more to 419 more)	ÅÅÅÅ
One-year OS rate (2)	Serious ^b	No	No	Serious ^c	None	18/113 (15.9%)	4/113 (3.5%)	5.29 (1.71 to 16.36)	127 more per 1000 (from 24 more to 340 more)	ÅÅÅÅ
Myelosuppression (14)	Serious ^a	No	No	No	None	46/504 (9.1%)	86/503 (17.1%)	0.46 (0.31 to 0.69)	84 fewer per 1000 (from 46 fewer to 111 fewer)	ÅÅÅÅ
Gastrointestinal toxicity (17)	Serious ^a	No	No	No	None	84/589 (14.3%)	142/587 (24.2%)	0.46 (0.33 to 0.64)	114 fewer per 1000 (from 72 fewer to 147 fewer)	ÅÅÅÅ
Hepatotoxicity (3)	Serious ^b	No	No	Serious ^c	None	4/100 (4%)	6/91 (6.6%)	0.51 (0.14 to 1.96)	31 fewer per 1000 (from 56 fewer to 56 more)	ÅÅÅÅ
Nephrotoxicity (2)	Serious ^b	No	No	Serious ^c	None	2/108 (1.9%)	3/108 (2.8%)	0.66 (0.11 to 4.07)	9 fewer per 1000 (from 25 fewer to 76 more)	ÅÅÅÅ
Chest pain(6)	Serious ^b	No	No	No	None	13/302 (4.3%)	20/302 (6.6%)	0.63 (0.31 to 1.3)	23 fewer per 1000 (from 45 fewer to 18 more)	ÅÅÅÅ

Fever (8)	Serious ^a	No	No	No	None	48/315 (15.2%)	51/315 (16.2%)	0.92 (0.59 to 1.45)	11 fewer per 1000 (from 60 fewer to 57 more)	ÅÅÅÅ
TRAEs (2)	Very serious ^d	No	No	Serious ^c	None	0/68 (0%)	0/68 (0%)	not pooled	not pooled	ÅÅÅÅ
Table 5b. The peripheral blood lymphocytes										
Indicators (Trials)	Quality assessment					MPE		Peripheral blood lymphocytes		Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	TPs	CIs	Odds ratios (95% CI)	SMD (95% CI)	
CD3 ⁺ T cells (8)	Serious ^a	No ^e	No	No	None	340	340	-	SMD 1.1 higher (0.54 to 1.66 higher)	ÅÅÅÅ
CD3 ⁺ CD4 ⁺ T cells(9)	Serious ^a	No ^e	No	No	None	395	395	-	SMD 1.93 higher (1.29 to 2.57 higher)	ÅÅÅÅ
CD4 ⁺ /CD8 ⁺ T cells ratio (6)	Serious ^a	No ^e	No	No	None	230	230	-	SMD 0.7 higher (0.36 to 1.04 higher)	ÅÅÅÅ
Note: OS rate: overall survival rate, SMD: standardized mean difference; ^a Trials had unclear risk, and some with high risk, but the result had good robustness. The evidence was downgraded by only one level; ^b all trials had no high risk. The evidence was downgraded by only one level; ^c the sample size for each indicator was less than 300 cases, and the evidence was rated down by one level; ^d all trials had high risk. The evidence was downgraded by only two levels; ^e the statistical heterogeneity was shown in the trials and sensitivity analysis with good robustness. Not downgraded.										

Figures

Figure 1

Articles retrieved and assessed for eligibility

Fig.3a Treatment success

Fig.3b Treatment failure

Fig.3c Quality of life

Figure 3

Clinical efficacy of thymic peptides with platinum

Figure 4

The analysis of OS rates between the two groups

Figure 5

Meta-analysis results of peripheral blood lymphocytes

Fig.6a Treatment success
($p=0.26$, 95%CI -0.41 to 1.43)

Fig.6b Treatment failure
($p=0.26$, 95%CI -1.43 to 0.41)

Fig.6c Myelosuppression
($p=0.08$, 95%CI -3.63 to 0.22)

Fig.6d Gastrointestinal toxicity
($p=0.13$, 95%CI -2.14 to 0.30)

Figure 6

The analysis of publication bias

Figure 7

TPs with platinum in MPE

Supplementary Files

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- [Supplementarymaterial3.Subgroupsanalysis.docx](#)
- [Supplementarymaterial4.PRISMAchecklist.doc](#)
- [Supplementarymaterial2.MetaanalysisresultsofADRs.docx](#)