Novel therapies for malignant pleural effusion: Anti-angiogenic therapy and immunotherapy (Review)

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Abstract. Patients with a variety of malignancies can develop malignant pleural effusion (MPE). MPE can cause significant symptoms and result in a marked decrease in quality of life and a poor prognosis. MPE is primarily considered as an immune and vascular manifestation of pleural metastases. In the present review, the existing evidence supporting the applicability of anti-angiogenic therapy and immunotherapy for the treatment of MPE was summarized. Patients with MPE have benefited from anti-angiogenic agents, including bevacizumab and endostar; however, no relevant prospective phase III trial has, thus far, specifically analyzed the benefit of anti-angiogenic therapy in MPE. Immunotherapy for MPE may be sufficient to turn a dire clinical situation into a therapeutic advantage. Similar to anti-angiogenic therapy, more clinical data on the efficiency and safety of immunotherapy for controlling MPE are urgently required. The combined use of anti-angiogenic therapy and immunotherapy may be a promising strategy for MPE, which requires to be further understood.

Contents

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1. Introduction

Tumor cells that have metastasized to the pleural space may result in malignant pleural effusion (MPE), which can develop in patients with various types of tumor, including breast, lung and hematological tumors (1,2). Dyspnea, chest pain and coughing are common symptoms of MPE (1). A significant decrease in quality of life (QoL) and a poor prognosis can be observed in patients with MPE (1).

Currently, the popular approaches for MPE management include pleuroscopy with subsequent chemical pleurodesis and thoracostomy (2). However, these treatment methods only provide symptomatic relief, with poor and unsatisfactory results (2). Furthermore, adverse effects such as chest pain, fever and dyspnea are often observed (3).

At present, the pathogenesis of MPE is not fully understood, but it is associated with impaired pleural fluid drainage (4). When metastatic cancer infiltrates the thoracic lymph nodes and pleura, the normal cycle of fluid secretion and absorption is interrupted, and the fluid is finally collected (4,5). MPE is the build-up of fluid in the pleural space, which contains immune cells, cancer cells and proteins (5). Cytokines and chemokines, including interleukin (IL)-10 (6), IL-6 (5), transforming growth factor (TGF)β (7) and vascular endothelial growth factor (VEGF) (8), are abundant in MPE. These factors serve an important role in MPE formation and can be used as therapeutic targets that enable MPE treatment. Among them, VEGF, which can prompt the formation of new blood vessels, is a key mediator of MPE pathogenesis (9). Several therapeutic strategies for MPE have focused on this protein (4,8,9). Furthermore, the pleural space in MPE is regarded as a tumor-tolerogenic milieu, which has a complex connection with immunosuppressive factors (10). However, this tumor-tolerogenic milieu can be reversed by immunotherapy, which has the potential to stimulate tumor-specific immune responses in the pleural space (10). Therefore, immunotherapy has been an area of special interest for MPE treatment (10).

MPE is primarily considered as an immune and vascular manifestation of pleural-metastasized cancer (11,12). Therefore, in the present review, the existing evidence supporting the applicability of anti-angiogenic treatment and immunotherapy for the treatment of MPE was summarized,

and the implications of the recent developments in MPE treatment were highlighted.

2. Anti-angiogenic treatment for malignant pleural effusion (MPE)

Role of VEGF in MPE. Large amounts of VEGF can be produced as tumor cells invade into the pleura, resulting in the acceleration of vascular permeability (13). The pleural fluid VEGF levels in MPE are significantly higher than those in effusions of benign disease, such as congestive heart failure and tuberculosis (2,8,14). In 2011, Fiorelli *et al* (9) studied 79 patients with unilateral PE. The levels of VEGF were demonstrated to be much higher in malignant than in benign exudates (9). In addition, in a study by Lieser *et al* (15), a 77-fold higher VEGF expression was observed in MPE compared with that in benign PEs. VEGF has therefore been suggested to be a diagnostic marker for MPE (16). Furthermore, patients with MPE with a high pleural VEGF level have been reported to have a significantly shorter survival than those with normal VEGF level (17,18).

The effects of VEGF are mainly mediated by endothelial cell receptors VEGF receptor-1 (VEGFR-1) and VEGFR-2 (19). VEGF binds to its receptors and induces downstream signaling, such as that of protein kinase C and mitogen-activated protein kinase; this process can induce vascular endothelium differentiation and proliferation, stimulate capillary sprouting and finally produce endothelial fenestrations and loss of junctional integrity, contributing to tumor growth and MPE development (4). Thus, the inhibition of VEGF activity with VEGF inhibitors is regarded as a promising approach for improving the management of MPE.

Bevacizumab treatment for MPE. Bevacizumab (Avastin®; Roche), the first humanized monoclonal antibody against VEGF, has been used to treat several types of tumor, including lung cancer and gynecological cancers (20-22). It can directly inhibit the proliferation and migration of vascular endothelial cells, promote the apoptosis of endothelial cells and suppress VEGF-induced neoangiogenesis and vascular permeability (23). Several studies have specifically researched the efficacy and safety of bevacizumab for the management of MPE (Table I). Among them, 6 are prospective studies (13,24-28), including two phase II trials conducted by Japanese groups (24,25). Unfortunately, there is still a lack of evidence from large phase III trials to confirm the effect of bevacizumab in the management of MPE.

Retrospective studies. The first retrospective study to investigate the efficacy of bevacizumab plus chemotherapy for patients with MPE was conducted by Kitamura *et al* (29). The aforementioned study analyzed data from 13 patients with MPE caused by non-small cell lung cancer (NSCLC) who received bevacizumab (15 mg/kg, intravenously) plus chemotherapy as first- or second-line treatment (29). As expected, an MPE control lasting >8 weeks was achieved in 12/13 patients (92.3%) (29). Similar results were obtained in other studies (3,30), which analyzed the records of patients treated for NSCLC-associated MPE, who consequently received bevacizumab (15 or 7.5 mg/kg, intravenously) plus chemotherapy. In one study, a total of 15/21 patients were responders, and a response rate of 71.4% was reported (30), while an MPE response rate of 81.0% was observed in the other study (3).

The delivery of bevacizumab directly to the pleural space is an alternative for MPE treatment. The intrapleural administration of bevacizumab for MPE treatment has been suggested in previous studies. Chen *et al* (31) demonstrated that the intrapleural infusion of bevacizumab was effective in controlling MPE without apparent toxicity. Jiang *et al* (32) came to a similar conclusion, with bevacizumab significantly improving the response rate and QoL of patients with MPE without notable adverse events (AEs). Song *et al* (33) demonstrated that, in patients with MPE treated with an intrapleural infusion of bevacizumab (200 mg) combined with pemetrexed (BP group) or cisplatin (BD group), the response rates in the BP and BD groups were 56.52 and 86.36%, respectively, and the overall survival (OS) time for both groups was both >10 months. These results suggested that the intrapleural infusion of bevacizumab combined with chemotherapy may be effective for patients with MPE (33).

Prospective studies. Two phase II trials analyzing the efficacy of bevacizumab in treating MPE were conducted on Japanese patients (24,25). The first study enrolled 23 patients with NSCLC with MPE who were treated with bevacizumab (15 mg/kg, intravenously) and carboplatin-paclitaxel (25). The primary endpoint of this study was an overall response rate (ORR) of 60.8% (25). The disease control rate (DCR), median progression-free survival (PFS) time and median OS time were 87.0%, 7.1 and 11.7 months, respectively (25). Furthermore, the addition of bevacizumab into the treatment protocol increased the MPE control rate from 78.3 to 91.3% (25). Correspondingly, the serum VEGF levels were decreased from 513.6 to 25.1 pg/ml following bevacizumab treatment (25). The second study focused on the treatment of bevacizumab with carboplatin-pemetrexed (24). A total of 28 patients with NSCLC-associated MPE were treated with carboplatin and pemetrexed with bevacizumab (15 mg/kg, intravenously) every 3 weeks (24). The control rate of MPE without pleurodesis at 8 weeks after treatment was defined as the primary endpoint (24). A total of 26/28 (92.8%) patients reached the primary endpoint (24). The median PFS, OS and median pleurodesis-free survival times were 8.2, 18.6 and 13.9 months, respectively (24). A high VEGF (≥100 pg/ml) level in the plasma, indicating a poor prognosis, was also observed (24).

Three Chinese prospective studies investigated the efficacy of intrapleural bevacizumab administration in patients with MPE (26-28). Wang *et al* (28) enrolled 33 patients with NSCLC with MPE who all received paclitaxel and bevacizumab (5 mg/kg, intrapleurally) once every 3 weeks for 12 consecutive weeks. The total response rate of this study reached 77% (28). The median OS and median PFS times were 22.2 and 8.4 months, respectively (28). Du *et al* (27) directly compared the efficacy of combined intrapleural therapy with bevacizumab (300 mg) and cisplatin versus cisplatin alone in controling MPE. A total of 70 patients with NSCLC with MPE were included, with 35 patients per group (27). The results revealed that the addition of bevacizumab improved the ORR from 50 to 83.3% (27). Additionally, patients in the bevacizumab + cisplatin group exhibited a higher QoL benefit and

Table I. Efficacy of anti-angiogenic therapy for MPE.

Authors, year	Study design (phase)	Antiangiogenic agent	N	Administration route	Treatment	MPE control, n/total n (%)	Long-term efficacy	Ref.
Usui *et al*, 2016	P (II)	Bevacizumab	28	IV	Bevacizumab + carboplatin	26/28 (92.9)[a]	mPFS: 8.2 months mOS: 18.6 months	(24)
Tamiya *et al*, 2013	P (II)	Bevacizumab	23	IV	Bevacizumab + carboplatin + paclitaxel	21/23 (91.3)[b]	mPFS: 7.1 months mOS: 11.7 months	(25)
Qi *et al*, 2016	P	Bevacizumab	24	IP	i) Paclitaxel; ii) paclitaxel + bevacizumab	i) 5/10 (50.0)[c]; ii) 11/14 (78.6)[c]	1 year survival rate: i) 20.8% ii) 45.8%	(26)
Du *et al*, 2013	P	Bevacizumab	70	IP	i) Cisplatin; ii) cisplatin + bevacizumab	i) 17/34 (50.0)[c] ii) 30/36 (83.3)[c]	mPFS: i) 4.5 months ii) 5.3 months	(27)
Wang *et al*, 2018	P	Bevacizumab	33	IP	Paclitaxel + bevacizumab	25/33 (75.8%)[c]	mPFS: 8.4 months mOS: 22.2 months	(28)
Nie *et al*, 2020	P	Bevacizumab	43	IP/IV	i) IV bevacizumab; ii) IP bevacizumab	i) 14/21 (66.7)[c] ii) 16/20 (80.0)[c]	NR	(13)
Masago *et al*, 2015	R	Bevacizumab	21	IV	Bevacizumab + chemotherapy	15/21 (71.4)[c]	NR	(30)
Tao *et al*, 2018	R	Bevacizumab	21	IV	Bevacizumab + chemotherapy	(90.0 at 12 months)[d]	mOS: 25.8 months	(3)
Kitamura *et al*, 2013	R	Bevacizumab	13	IV	Bevacizumab + chemotherapy	12/13 (92.3)[b]	mPFS without re-accumulation of MPE: 312 days	(29)
Jiang *et al*, 2017	R	Bevacizumab	86	IV	i) Bevacizumab + EGFR-TKI; ii) bevacizumab + chemotherapy	i) 42/47 (89.4)[c]; ii) 25/39 (64.1)[c]	mPFS: i) 6.3 months; ii) 4.8 months	(35)
Song *et al*, 2018	R	Bevacizumab	45	IP	i) Bevacizumab + pemetrexed; ii) bevacizumab + cisplatin	i) 19/22 (86.4)[c]; ii) 13/23 (56.5)[c]	mPFS: i) 5.4 months; ii) 4.0 months mOS: i) 10.5 months; ii) 10.3 months	(33)
Jiang *et al*, 2016	R	Bevacizumab	43[e]	IP	i) Bevacizumab + cisplatin; ii) cisplatin	i) 16/20 (80.0)[c]; ii) 11/23 (47.8)[c]	mPFS: i) 5.4 months; ii) 4.0 months mOS: i) 10.5 months; ii) 10.3 months	(32)
Wang *et al*, 2005	P	Endostar	128	IP	i) Endostar + pemetrexed + cisplatin; ii) pemetrexed + cisplatin	i) 62/66 (93.9)[b]; ii) 49/62 (79.0)[b]	1-year survival rate: i) 78.79% ii) 74.19%	(37)
Zhao *et al*, 2014	P	Endostar	45[e]	IP	i) Endostar + cisplatin; ii) cisplatin	i) 18/23 (78.3)[c]; ii) 9/22 (40.9)[c]	NR	(39)

Table I. Continued.

Authors, year	Study design (phase)	Antiangiogenic agent	N	Administration route	Treatment	MPE control, n/total n (%)	Long-term efficacy	Ref.
Matsumorii *et al*, 2006	P (II)	Vandetanib	20	Oral	Vandetanib	-	mOS: 10.6 months	(41)
Mulder *et al*, 2014	P (II)	Cediranib	12[e]	Oral	i) Cediranib administrated on day 1 ii) cediranib administrated on day 29	-	mOS: i) 73 days; ii) 24 days	(44)

[a]MPE control defined as not needing pleurodesis at 8 weeks of treatment; [b]MPE control defined as no re-accumulation of MPE for ≥8 weeks after the start of treatment; [c]MPE control defined as complete response and partial response/incomplete relief; [d]MPE control defined as the percentage of patients who did not experience re-accumulation of pleural fluid for 4 weeks from the time of the catheter being removed. [e]Including patients with symptomatic malignant ascites and MPE. MPE, malignant pleural effusion; mOS, median overall survival; mPFS, median progression-free survival; P, prospective; R, retrospective; IV, intravenous; IP, intraperitoneal; EFGR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; NR, not reported.

a higher decrease in pleural VEGF levels (27). Another group of 24 patients with NSCLC was enrolled in a similar study by Qi *et al* (26). A total of 14 patients in that study received intrapleural infusion of paclitaxel and bevacizumab (5 mg/kg), and the remaining 10 received paclitaxel alone (26). The results revealed that combination therapy significantly decreased the MPE levels, with an overall efficacy rate of 78.6% (a 29% increase compared with paclitaxel alone) (26). The addition of bevacizumab also improved the 1-year survival rate from 20.8 to 45.8% (26).

In 2017, Zongwen *et al* (34) performed a meta-analysis that included 11 randomized controlled trials (RCTs) with a total of 769 patients with lung cancer, to investigate the efficacy and safety of bevacizumab in controling MPE. All the studies in the meta-analysis were conducted by Chinese groups and most of them (10/11) were published in Chinese (34). This meta-analysis provided further evidence to support the administration of bevacizumab via intrapleural injection in patients with MPE (34). As compared with platinum alone, the addition of bevacizumab significantly increased the ORR (P=0.003), decreased the incidence of chest pain (P<0.001) and relieved dyspnea in patients (P=0.002) (34).

Intrapleural or intravenous infusion. The aforementioned studies indicated that the combination of bevacizumab and chemotherapy may be effective for controlling MPE, although the sample sizes of these studies were small. For MPE management, bevacizumab can be administered intravenously or intrapleurally. However, the optimal administration route of bevacizumab has not yet been defined. Theoretically, compared with intravenous infusion, intrapleural infusion has some advantages, including the site-specific concentration of therapeutic agents with lower overall doses (10). Furthermore, the closed nature of the pleural space makes it an ideal site for intrapleural infusion (10). A recent randomized clinical study compared the efficiency and safety of intrapleural (7.5 mg/kg) and intravenous (7.5 mg/kg) infusion of bevacizumab in the management of MPE (13). Hypertension, epistaxis and proteinuria are common AEs associated with bevacizumab, which occurred more often in the intravenous group compared with in the intrapleural one (13). A higher ORR and a longer median duration of response were also observed in the intrapleural group, but the difference between the two groups was not statistically significant (13). The reason for this may be that the sample size of the study was too small (n=43). Therefore, large studies are required to confirm these results.

Future directions and ongoing trials. Currently, to the best of our knowledge, there are no prospective phase III studies specifically focusing on the benefit of bevacizumab combined with chemotherapy in MPE, which is a major issue. In addition, most of the aforementioned studies, whether prospective or retrospective, were conducted by Chinese and Japanese groups, which may lead to geographical and ethnical differences in the results. Therefore, data from other ethnic groups are required. Furthermore, there is a lack of data concerning rare tumor-driver mutations in patients with MPE caused by NSCLC. Jiang *et al* (35) retrospectively investigated 86 patients with NSCLC with MPE who had developed acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy. In the aforementioned study, patients who were treated with bevacizumab

and EGFR-TKIs had a longer PFS and higher curative efficacy rate for MPE, indicating that this combination therapy may be a valuable treatment option for patients with MPE (EGFR mutation-positive) caused by NSCLC (35).

Treatment of MPE with other anti-angiogenic drugs

Recombinant human endostatin. Endostatin is an endogenous inhibitor of angiogenesis, which can interfere with the pro-angiogenic effects of growth factors and inhibit angiogenesis in a wide range of tumors, including lung, gastric and colon cancer (36-39). Similarly to VEGF, endostatin is also a potential prognostic factor for MPE (18,36). To enhance the solubility and stability of endostatin, recombinant human endostatin was engineered (a 9-amino acid sequence was added to the N-terminal of the protein) and termed endostar (16). Based on the results of a phase III study (37), endostar was listed as a first-line drug for the treatment of NSCLC in Chinese patients.

For patients with MPE, endostar was effective when administered via intrapleural infusion (37-39). A Chinese group evaluated the efficacy of endostar combined with cisplatin/pemetrexed chemotherapy for elderly patients with MPE (38). A total of 128 patients with lung adenocarcinoma with MPE were randomly assigned to receive chemotherapy plus endostar (treatment group) or chemotherapy alone (control group) (38). Compared with chemotherapy alone, endostar plus chemotherapy significantly improved MPE control rates (93.94 vs. 79.03%; P=0.013) and decreased recurrence rates (9.68 vs. 30.61%; P=0.005) with tolerable side effects (38). Similar results were obtained in a smaller RCT that included 45 patients with MPE or ascites (39). Furthermore, Biaoxue *et al* (40) conducted a meta-analysis based on 13 RCTs that included 1,066 patients with MPE, demonstrating that the addition of endostar to chemotherapeutic agents can significantly improve ORR and DCR, indicating that endostar is effective in treating MPE (40). However, one of the limitations of the aforementioned meta-analysis was that all included studies were from China. To the best of our knowledge, no data are available from outside China. Therefore, although endostar appears to be promising in controlling MPE, it still requires further investigation before it can be recommended for clinical application.

Anti-angiogenic TKIs. In addition to VEGF, other pro-angiogenic factors, such as TGF, platelet derived growth factor (PDGF) and fibroblast growth factor, have been associated with the development of PEs (4). Anti-angiogenic TKIs, which block the kinase activity of receptors, have been explored for the treatment of MPE. In *in vitro* and murine models of MPE, anti-angiogenic TKIs, such as lenvatinib, vatalanib and nintedanib, have been reported to control MPE (41,42).

Data from clincal trials evaluating the efficacy of EGFR-TKIs in patients with MPE are limited, with only two phase II trials (43,44). The first study enrolled 20 patients with NSCLC to evaluate the efficacy of vandetanib (VEGFR- and EGFR-TKI) for MPE control (43). The patients received oral vandetanib at a dose of 300 mg once a day for a maximum of 10 weeks, and time to pleurodesis was the primary endpoint (43). The results revealed that vandetanib was well tolerated, but it did not significantly decrease time to pleurodesis (43). The second study enrolled 12 patients with malignant ascites or MPE to assess the palliative value of cediranib (VEGF-TKI) (44). The primary endpoint was puncture-free survival, which was defined as the time from the start of the study to the time that paracentesis or thoracentesis were first needed, or the time of death (44). As expected, cediranib treatment significantly increased puncture-free survival with an acceptable toxicity profile (44). This phase II trial was the first study to show the palliative effects of oral VEGFR-TKI in patients with malignant effusions (44). Although sorafenib (RAF-, PDGFR- and VEGFR-TKI) has been reported to decrease MPE in one patient with advanced thyroid carcinoma (45), no further evidence has been acquired to support this treatment strategy.

The clinical trials on TKIs in this context are limited, and more data are urgently required. The other important issue is that most anti-angiogenic TKIs are administrated intraorally. Therefore, whether safe doses of anti-angiogenic TKIs comprise therapeutic concentrations for MPE through oral administration needs to be further investigated.

Another anti-VEGF antibody. In addition to bevacizumab, ramucirumab is another anti-VEGF antibody used in a clinical setting. The PLEURAM study is an ongoing phase II trial evaluating the efficacy and safety of ramucirumab in controling MPE (46). The study plans to enroll 15 patients with NSCLC and ramucirumab (10 mg/kg) combined with docetaxel (60 mg/m^2) will be administered to each patient every 3 weeks (46). The MPE control rate at 8 weeks will be the primary endpoint (46).

3. Immunotherapy for MPE

Research on MPE control has also shed light on immunotherapy. Given the potential for stimulating tumor-specific immune responses in the pleural space, intrapleural immunotherapy has been an area of notable interest for MPE treatment (47). Cytokines, which can be used as potent immunostimulatory agents to counter tumor-mediated immune tolerance and T-cell exhaustion, have long been investigated for the treatment of MPE. Adoptive therapy with chimeric antigen receptor (CAR) T cells or tumor-infiltrating lymphocytes (TILs), most often using the patients' own immune cells to treat their cancer, are also being examined for use in MPE treatment. Other treatments for MPE, such as immunogene therapy and oncolytic virotherapy, are currently underdeveloped.

Cytokine-based immunotherapy

IL-2 treatment. IL-2, which is produced primarily by activated CD4$^+$ and CD8$^+$ T cells, may act as a growth factor for all T-cell subsets (48), which may change a non-inflamed tumor into an inflamed tumor, thereby increasing the sensitivity of that tumor to further immune attack (49). IL-2 has been used to control MPE through intrapleural infusion for a long time. As early as in 1993, a group from France performed a phase I study to determine the safety and efficacy of intrapleural recombinant IL-2 infusion in 22 patients with MPE (50). The results revealed that 10/22 patients achieved responses during the course of the treatment, including 1 case of complete remission (CR) and 9 of partial remission (PRs) (50). Subsequently, other phase I/II studies on the intrapleural infusion of recombinant IL-2 for patients with MPE had an ORR

of 21.7-22.0% (51,52), except for a phase I study conducted by Suzuki *et al* (53) in 1993, which had a total response rate of 100.0% (11/11 patients). The toxicity of IL-2 was found to be dose-dependent and the most common AE was fever; transient abnormal renal function, eosinophilia and flu-like syndrome were also observed (51-53). A meta-analysis of 18 Chinese clinical trials demonstrated that the thoracic injection of IL-2 and cisplatin led to a higher ORR, DCR and QoL than cisplatin alone in patients with MPE (54). Furthermore, Hu *et al* (55) revealed that IL-2 administration decreased the expression levels of programmed cell death protein 1 (PD-1), increased those of granzyme B and interferon (IFN)γ and enhanced the proliferation of $CD8^+$ T cells in MPE. These results indicated that the exhaustion phenotype of $CD8^+$ T cells, which contributes to tumor immune escape and metastasis, may be reversed by IL-2 treatment. Therefore, Hu *et al* (55) provided new evidence supporting the use of IL-2 in MPE.

To the best of our knowledge, no studies have been performed in the past 3 years on the role of IL-2 in treating MPE, particularly outside China. Although IL-2 treatment is not a mainstay of MPE treatment, IL-2 should be reexamined in this setting for novel combination therapy. For example, IL-2 may be used in a rationally designed combination therapy with immune checkpoint inhibitors (ICIs), due to its role in PD-1 expression (55). Other interleukins, such as IL-10 (56), IL-17 (57) and IL-27 (58), may also have the potential to inhibit the development of MPE, but they require further exploration.

Tumor necrosis factor-α (TNF-α) treatment. Similar to IL-2, TNF-α has been studied for its potential role in MPE management. In a study by Li *et al* (59), 102 patients with lung cancer with MPE received a single dose of recombinant human TNF-α (rhu-TNF) following maximum drainage of the pleural cavity. The results revealed that intrapleural infusion of rhu-TNF sufficiently controlled MPE with a response rate of 81.37% and that the AEs of this treatment were well tolerated (59). The data demonstrated that the short-term efficacy of TNF-α treatment was non-inferior to that of anti-angiogenic treatment, such as bevacizumab (59). However, the study was limited in that it was a retrospective trial.

IFN treatment. IFNs are a family of cytokine mediators. Type I IFNs, such as IFN-α and IFN-β, are known to stimulate the immune system and inhibit tumor cell proliferation (60). Due to their role in the immune system, IFNs are being investigated and used in various respiratory disorders, including MPE (60). In 1993, Goldman *et al* (61) evaluated the safety and efficacy of intrapleural IFN-α2b in patients with MPE. A total of 14/20 (70%) evaluable patients exhibited responses lasting for a median of 6 months, including 8 cases of CR and 6 of PR (61). The response rate of IFN-α2b treatment in that study was encouraging. However, a prospective randomized trial published in 2004 revealed that standard bleomycin chemotherapy was more effective than IFN-α2b in MPE, with patients in the bleomycin group exhibiting a higher response rate and longer survival (62). Since then, studies on IFN-α2b in MPE treatment have been rare.

IFN-β is another type I IFN that has been investigated for MPE treatment. In total, 10 patients with malignant pleural mesothelioma (MPM) or MPE were enrolled in a phase I study to evaluate the safety and feasibility of a single-dose intrapleural IFN-β gene transfer using an adenoviral vector expressing IFN-β (Ad.IFN-β) (63). Intrapleural Ad.IFN-β was generally well tolerated, with 7/10 patients responding to this treatment method (63), which indicated that intrapleural Ad.IFN-β may be a potentially useful approach for the treatment of MPE. A follow-up phase I trial was conducted 3 years later, and 7 patients with MPE and 10 with MPM were enrolled to receive 2 doses of intrapleural Ad.IFN (64). After the first dose, the pleural IFN-β levels were significantly elevated; however, the elevated levels were not sustained, falling to <1 ng/ml after the second dose (64). These unsatisfactory results may have been associated with the rapid development of neutralizing antibodies against the adenoviral vector after the second dose (64).

Intrapleural immunogene therapy. The aforementioned Ad.IFN-β treatment is an example of using intrapleural immunogene therapy to treat MPE (63,64). For intrapleural immunogene therapy, viral vectors are often used, functioning as an '*in-situ* vaccination' (10). Based on the expression of the coxsackie-adenovirus receptor on the tumor cell surface, adenovirus-based viral vectors can selectively infect tumor cells (10). After reaching the pleural space, Ad.IFN efficiently transfects tumor cells. As a result, large concentrations of IFN are produced, serving a role in immunity stimulation and tumor inhibition (65).

Another example of the use of intrapleural immunogene therapy for the treatment of MPE is from a phase I study conducted by Aggarwal *et al* (66). A total of 19 patients with MPE caused by MPM, NSCLC and breast cancer were enrolled to evaluate the tolerability and efficacy of intrapleural gene-mediated cytotoxic immunotherapy (GMCI) (66). GMCI is an immune strategy that consists of two steps: First, an adenovirus-mediated herpes simplex virus thymidine kinase gene (Ad.V-tk) is administered via intrapleural delivery; next, the anti-herpetic drug valacyclovir is administrated the day after Ad.V-tk infusion (66). Following intrapleural injection, Ad.V-tk efficiently transfected tumor cells to express the thymidine kinase gene, resulting in the production of a large amount of nucleotide analogs, which can interrupt normal DNA replication and trigger tumor cell death, consequently releasing tumor neoantigens (66). It has been revealed that tumor neoantigens from dying tumor cells can also induce antitumor immune responses (10). The results of Aggarwal *et al* (66) demonstrated that GMCI was safe and well tolerated in patients with MPE, with an encouraging efficacy (DCR of 71%).

ICIs. Currently, ICI treatment is the mainstay of anticancer immunotherapy. Agents that target cytotoxic T lymphocyte-associated protein 4 (CTLA-4), such as ipilimumab, and PD-1, such as nivolumab, are two major classes of ICIs (67). PD-1, a receptor on the surface of T cells, binds to its ligand (PD-L1 or PD-L2) to decrease T-cell activity, causing apoptosis in cytotoxic T cells (68). CTLA-4 is a key negative regulator of T-cell responses, which can restrict the antitumor immune response (69). ICIs can discrupt these two immunosuppressive signaling pathways, resulting in improved survival outcomes

Table II. Major ongoing clinical trials of anti-angiogenic therapy and immunotherapy in the treatment of MPE.

Number	Phase	Tumor type	Country	Status	Planned number of patients	Drug	Primary outcomes
NCT02942043	II	NSCLC	China	Recruiting	87	Bevacizumab	Objective response rate
NCT02054078	II	Any tumor	China	NR	183	1. Bevacizumab 2. Pulvis talci	Changes in chest drainage
NCT02005120	II	NSCLC	China	NR	20	1. Bevacizumab 2. Recombinant human endostatin	Objective response rate
jRCTs07119001	II	NSCLC	Japan	NR	15	Ramucirumab	The pleural effusion control rate at eight week
NCT04123886	I	Any tumor	China	Recruiting	12	Recombinant Human TRAIL-Trimer Fusion Protein (SCB-313)	Dose limiting toxicity
NCT03869697	I	Any tumor	Australia	Recruiting	16	Recombinant Human TRAIL-Trimer Fusion Protein (SCB-313)	Dose limiting toxicity
NCT03736122	I/II	Any tumor	Australia	Not yet recruiting	58	BSG-001 (an immune-modulator that primarily exerts its effect via Toll-like receptor)	1. Safety and tolerability 2. Change in fluid volume
NCT03597009	I/II	Metastatic cancer	USA	Recruiting	24	1. Talimogene laherparepvec 2. Nivolumab	Phase 1: Treatment-related adverse events Phase II: Resolution of MPE
NCT02429726	II	Any tumor	China	NR	90	Recombinant adenoviral human p53 gene	Objective response rate
NCT01997190	I	Any tumor	USA	Active, not recruiting	19	AdV-tk	Safety
NCT01766739	I	Lung cancer	USA	Active, not recruiting	18	GL-ONC1 (a genetically modified vaccinia virus)	Maximum tolerated dose
NCT02414269	I/II	Malignant pleural disease	USA	Recruiting	179	Mesothelin-targeted T cells	Phase I: Safety Phase II: Clinical benefit rate
NCT03054298	I	Mesothelin-expressing cancer	USA	Active, not recruiting	-	Lentiviral transduced huCART-meso cells	Safety

MPE, malignant pleural effusion; NSCLC, non-small cell lung cancer; TRAIL, TNF-related apoptosis-inducing ligand; AdV-tk, adenovirus-mediated herpes simplex virus thymidine kinase; huCART cells, humanized chimeric antigen receptor-modified T cells; NR, not reported.

for patients with solid tumors, such as NSCLC, melanoma and colorectal cancer (70-72).

However, there is currently almost no available data on the response of patients with MPE to ICIs. The efficacy of ICIs in MPE remains to be determined by clinical trials. Recently, two retrospective studies suggested that the presence of MPE in patients is a negative predictor of anti-PD-1 antibody efficacy (73,74). However, these results did not suggest that ICIs are not valid for MPE treatment. In a study by Grosu *et al* (75), a high concordance in PD-L1 expression was identified between histological specimens and matched pleural fluid from patients with NSCLC, suggesting that, if the primary tumor is sensitive to anti-PD-1 treatment, MPE may also be affected by this treatment. The role of the PD-L1/PD-1 pathway in MPE development has also been explored previously (76). In patients with lung cancer with MPE, Prado-Garcia *et al* (76) found that tumor-responding $CD8^+$ T cells were not completely differentiated into effector cells, which were negative regulated by PD-L1, so that the PD-L1/PD-1 pathway could promote the dysfunction of tumor-responding T cells from MPE.

Oncolytic virotherapy. As a promising therapeutic modality for the treatment of cancer, oncolytic virotherapy has attracted more attention in recent years. Oncolytic virotherapy infects malignant tissues with tumor-specific viruses, causing the lytic destruction of solid tumors (77). Tumor cell lysis caused by viral infection can induce antitumor immune responses (78). A total of 13 patients with MPM were enrolled in a phase I/IIa trial to receive intrapleural oncolytic herpes simplex virus 1716; the systemic immune responses observed further indicated that an intrapleural oncolytic virus could induce antitumor immune responses, which may serve a role in MPE treatment (79). In a previous preclinical study, oncolytic virotherapy using a tumor-specific vaccinia virus represented a novel and promising treatment modality for the treatment of MPE in tumor mouse models (77). However, clinical evidence on this remains limited. Certain phase I/II clinical trials of oncolytic virotherapy in MPE are ongoing (Table II). NCT01766739 is an ongoing phase I study on the intrapleural administration of GL-ONC1, a genetically modified vaccinia virus, in patients with MPE, aiming to assess the safety and efficacy of this treatment method. NCT03597009 is an ongoing phase I/II trial to evaluate the feasibility of adminstering oncolytic virus talimogene laherparepvec (via intrapleural perfusion) and nivolumab (intravenously) in patients with MPE; it is the first clinical trial to combine oncolytic virotherapy and ICIs in MPE treatment.

Dendritic cell (DC) vaccination. In the immune system, DCs are the dominant antigen-presenting cells (80). DC-based immunotherapy is a promising cancer treatment method in various types of cancer, including MPE (81). A previous study enrolled 8 patients with late-stage lung cancer who were then injected with autologous DCs generated by culturing adherent mononuclear cells from MPE (81). No grade II/III toxicity was observed (81). Following DC vaccination, an increase in T-cell responses against tumor antigens was observed in 6/8 patients (81). Another 5 patients with MPE or malignant ascites, who were resistant to standard chemotherapy, were treated with combined immunotherapy using monocyte-derived DCs, activated lymphocytes and low-dose OK-432 (a streptococcal preparation) (82). Effusion production was decreased in all of the patients and the mean OS time was >9 months (82). Furthermore, the presence of inflammatory DCs (infDCs) in patients with NSCLC with MPE has been recently observed (83). infDCs represent a distinct human DC subset that can induce T helper 1 cell differentiation in the presence of Toll-like receptor agonists (83). This promising finding may provide a new approach for MPE treatment.

CAR - cell treatment. CAR T-cell treatment is another research hotspot in cancer immunotherapy. This technique involves CAR T-cell receptors being specifically engineered to eradicate tumors by recognizing surface proteins expressed on tumor cells (84). In previous studies, CAR T-cell treatment has had substantial clinical success in treating patients with hematological malignancies (85-87). Currently, a growing number of clinical trials of CAR T-cell treatment have focused on solid tumors, targeting surface proteins, including carcinoembryonic antigen, mesothelin, fibroblast activation protein (FAP) and human epidermal growth factor receptor 2 (HER2) (84,88-90). However, to the best of our knowledge, no clinical trial has specifically targeted MPE, despite the local application of CAR T-cell treatment being an attractive approach. A phase I study of intrapleural CAR T cells directed against FAP in patients with MPM with MPE has been completed, but the results have not yet been published (NCT01722149). NCT02414269 and NCT03054298 are two ongoing trials on intrapleural and/or systemic mesothelin CAR T-cell delivery for patients with MPM (Table II). As patients with MPM often present with PE (91), the aforementioned studies will also provide a foundation for controlling MPE via CAR T-cell delivery. FAP and mesothelin are tumor-specific antigens (TSAs) expressed on the surface of MPM cells (92). In order to investigate the efficacy of CAR T-cell delivery for MPE secondary to NSCLC or breast cancer, other targeted TSAs, such as EGFR and HER2, should be investigated.

TIL treatment. TILs are cell clusters with an antigen effect resulting from tumorigenesis (93). T lymphocytes, B lymphocytes and natural killer lymphocytes are the main components of TILs (93). Among them, $CD8^+$ T lymphocytes mainly exert an anticancer activity (94). In a retrospective study, 27 patients with MPE and ascites were treated with either cisplatin (60 mg) or TILs (100 ml) (95). Compared with patients who received cisplatin, patients who received TILs had a higher ORR (83.33 vs. 33.33%) and DCR (71.43 vs. 28.57%), without severe adverse effects (95). Therefore, TILs may represent a promising treatment method for MPE, and should be investigated further.

4. Conclusion and future research direction

The significant progress that has been made in targeted cancer treatment and immunotherapy over the last decade has rendered the identification of novel treatment methods to treat, rather than palliate, MPE. Since angiogenesis serves a key role in MPE development, attention for MPE treatment has inevitably been focused on anti-angiogenic treatments. Patients with MPE have benefited from antiangiogenic agents,

including bevacizumab and endostar. However, no relevant prospective phase III trial has, thus far, specifically analyzed the benefit of anti-angiogenic therapies in MPE. In addition, the majority of clinical studies that have focused on this field are from East Asia, which indicates that this treatment strategy for MPE has not yet attracted worldwide attention. The reasons may due to the following aspects: Firstly, bevacizumab and endostar are more often used in East Asia; secondly, East Asia has a large number of patients with MPE that need anti-angiogenic therapy. More clinical data on anti-angiogenic therapies for MPE control are warranted.

The advent of effective immunotherapy with ICIs, as well as adoptive cell therapies for lung cancer and other malignancies, has led to a renewed examination of local and systemic immunotherapies for patients with MPE. Prior strategies, such as cytokine-based immunotherapy, have been successfully used in MPE treatment. However, these strategies have not been as effective as expected. Since MPE has an immunosuppressive microenvironment, strategies involving the activation of the adaptive immune response and inhibition of tumor immune escape mechanisms may serve a role in MPE control. Therefore, treatment with ICIs, CAR T cells, immunogene therapy or oncolytic viruses may be sufficient to turn a dire clinical situation into a therapeutic advantage. Similar to anti-angiogenic therapy, more clinical data on the efficacy and safety of immunotherapy for MPE control are urgently required.

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Authors' contributions

DH and RD made substantial contributions to the conception and design of the study, assessed the authenticity of the data and wrote the manuscript. QW and LC contributed to the study design and assisted in the literature search for this review article. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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