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REVIEW

Progress in Mechanistic Research and the Use of Traditional Chinese Medicine in Treating Malignant Pleural Effusion

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Abstract: Malignant pleural effusion (MPE) is characterized by the accumulation of fluid in the chest cavity, secondary to metastasis from a primary pleural tumor or malignant neoplasms originating from other anatomical sites. MPE is associated with a poor prognosis. Consequently, timely and effective prevention and management of MPE are critical. In Western medicine, the treatment of MPE primarily involves procedures such as surgical puncture for drainage, pleural fixation, chemotherapy, and targeted therapy. In contrast, traditional Chinese medicine (TCM) offers therapeutic modalities including oral decoctions, thoracic perfusion with herbal injections, topical applications of medicinal pastes, and acupoint therapies. The TCM approaches have demonstrated satisfactory clinical outcomes. Advances in the study of TCM for managing MPE in lung tumors are expected to yield a wealth of therapeutic strategies, facilitating the development of more optimized clinical treatments.

Keywords: malignant pleural effusion, mechanism, prevention and management, traditional Chinese medicine, lung tumors

Introduction

Pleural effusion (PE) refers to the abnormal accumulation of fluid in the pleural cavity. Potential etiologies encompass cardiac insufficiency, malignant tumors, tuberculous pleurisy, pneumonia, liver cirrhosis, and nephrotic syndrome, among others. Based on the characteristics of pleural effusion, it can be categorized into exudative, transudative (serous or hemorrhagic), hemothorax, empyema, and chylothorax. A critical challenge in the differential diagnosis of pleural effusion is the early identification and differentiation between benign and malignant types. Early intervention for benign pleural effusion can lead to successful resolution and minimize the risk of complications. Meanwhile, early management of malignant pleural effusion (MPE) can enhance the quality of life and improve survival rates in patients with advanced malignancies.[1,2]

The objective of this paper is to present a thorough and up-to-date overview of the pathogenesis of MPE and the use of traditional Chinese medicine (TCM) for the treatment and management of MPE. We expect that this review will help clinicians personalize healthcare for patients with MPE and improve the survival and quality of life of patients with cancer.

Profile of Malignant Pleural Effusion

Malignant pleural effusion occurs because of a primary pleural malignancy or metastasis of a malignant tumor to the pleura from another site. The diagnosis of MPE can be confirmed by detecting malignant tumor cells in a pleural effusion sample or pleural biopsy tissue.[3] Almost all malignant tumors can cause MPE as a complication with disease progression.[4] The incidence of MPE associated with lung cancer (35%), breast cancer (23%), and lymphoma (10%) has been reported to exceed 60%.[5] Median patient survival in such cases is only 3–12 months.[6] Clinical management of

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MPE involves several aspects, including local and systemic therapies such as thoracentesis, chest tube drainage, pleural fixation, chemotherapy, and targeted therapy.[7] However, these remedies have limited effectiveness.

Physiologic Significance of Pleural Effusion

The normal chest cavity contains approximately 0.26 mL/kg of liquid, which acts as a lubricant in the chest space to reduce the friction from the wall to the guts during respiration and maintain negative pressure to avoid lung collapse. The volume of pleural fluid depends on hydrostatic pressure, mesothelial cell activity, and lymphatic drainage.[8,9] In a healthy body, luminal fluid secretion and absorption are always maintained in a state of equilibrium. Fluid accumulation occurs if fluid production exceeds the ability of the lymphatic vessels to absorb it, due to factors such as increased production, decreased absorption, or both.[10] Consequently, when the amount of pleural fluid produced is greater than the amount absorbed, the fluid accumulates in the chest cavity.

Pathogenesis and Molecular Mechanisms of MPE

The etiology of MPE has not been fully elucidated to date. One common mechanism leading to the occurrence of MPE is the blockage of the nodes of the mural pleura and the resultant lymphatic obstruction caused by the growth and proliferation of tumor cells into the thoracic cage.[11] Primary or metastatic lesions of the pleura and inflammatory stimuli can lead to increased capillary permeability and abnormal angiogenesis, causing the occurrence of PEs.[7] A large number of cytokines and chemokines have been implicated in the formation of malignant effusions, including vascular endothelial growth factor (VEGF),[12] interleukin (IL)-1β,[13] transforming growth factor (TGF)-β1,[14] IL-6, IL-8, and IL-10.[15] MPE also contains a host of immunologic cells and cytokines with immunosuppressive properties, which contribute to tumor immune escape and promote pleural tumor growth and MPE formation.[16]

Direct Invasion or Hematogenous Metastasis

The pleura may be penetrated by lymphatic spread and/or invasion of tissue lesions in the diaphragm, pericardium, chest wall, and other adjacent organs. Autopsy data show that tumor cells disperse into the pleura predominantly via blood circulation and first invade the visceral pleura. As a result, tumor cells may spread in an adherent manner or as detached cancer cells floating in fluid secondary to pleural spread.[17] Tumor cells adhere to the pleural mesh, bypass the pleural immunity mechanism, and infiltrate pleural tissue to access nourishment and growth factors upon reaching the pleural wall layer. In patients with MPE, impaired macrophage and lymphocyte function, along with the production of pro-inflammatory factors and pro-tumor mediators, create complex interactions between cancer cells and their hosts. These processes contribute to an immune-suppressing microenvironment within the pleura. Even though they are not attached to pleural structures, floating tumor cells can generate lesions elsewhere in the pleural cavity, indicating that malignant tumors can enter the pleura through direct invasion or hematogenous metastasis and disrupt the pleural barrier function to cause PE.[16]

Involvement of Lymphatic Vessels

Lymphatic vessels constitute an important system involved in fluid reflux. Fluid arrives in the cavity through the pleural wall capillaries, and since the pressure slope for the motion of fluid in the plenum is almost zero, peritoneal effluent is primarily aspirated by lymph vessels through the lymphatic micropores of the mural pleura.[11] Obstruction of lymphatic drainage in the mural pleura is the primary mechanism underlying the formation of MPE. This obstruction occurs through a combination of compression by the lung cancer mass and metastasis through the lymphatic channels, thus causing MPE.[18]

Role of Angiogenesis in MPE

The typical clinical symptom of MPE is compression of lung tissue, and the consequent respiratory and circulatory dysfunction seriously affect patients' quality of life and can even be life-threatening.[17] Angiogenesis and vascular remodeling are key pathophysiological stages in the creation of MPE.[16] Several investigations have revealed that a hyper-permeable pleural wall or internal vasculature and the tumor vasculature play pivotal roles in the pathobiology of

MPE.[7,17,19] Pleural tumor cells secrete a diverse array of vasoactive mediators, including angiopoietin and/or VEGF, leading to excessive angiogenesis and invasion of the thoracic cavity. The vascular hyperpermeability associated with pleural malignancy and the anti-inflammatory host reaction induced by tumor cells in the cavity have been linked to the etiology of MPE.[20,21]

Cytokines Released by Tumor Cells

MPE is a high-protein fluid that accumulates in the presence of cytokines and growth factors with pro-inflammatory, anticancer, and angiogenic characteristics (eg, VEGF) and suppressor factors (eg, IL-10).[15,22] This indicates that MPE may create a nutritious microenvironment that favors the growth of tumors while simultaneously inhibiting the immune system's anti-tumor activity.

Role of Angiogenic Factors in MPE

Angiogenic factors are known to influence the kinetic basis of PE development since they can also induce leakages in the vasculature. Angiogenic cytokines such as basic fibroblast growth factor (bFGF), VEGF, and angiopoietin are likely initiators of MPE, since they have been correlated with the onset of neovascularization, vascular permeability, and bleeding, in the process of inflammation and in tumor progression.[23]

i) Vascular endothelial growth factor: VEGF is an essential angiogenesis-stimulating factor. Tumors invading the chest wall secrete vast quantities of VEGF, which increases the permeability of blood vessels.[24] VEGF levels in patients with MPE have been shown to be significantly higher than those in patients with other diseases such as congestive heart failure or pulmonary tuberculosis.[25–28] In one study investigating 79 cases of unilateral PE,[29] the VEGF levels were clearly greater in malignant tumors than in benign tumors. In another study, VEGF expression in MPE was 77-fold greater than that in benign PE.[30]

Furthermore, MPE with elevated pleural VEGF levels has been shown to be associated with significantly lower survival rates than MPE with normal VEGF levels.[31,32] The effects of VEGF are primarily mediated by VEGF receptors 1 and 2 (VEGFR-1 and VEGFR-2, respectively) [19]. VEGF is recruited by its receptor and activates downstream signals including protein kinase C and mitogen-activated protein kinase (MAPK), which triggers vascular endothelial proliferation and differentiation, stimulates endothelial apoptosis, and eventually leads to endothelial apertures and loss of barrier cohesion, promoting the initiation of tumor growth and progression of MPE.[33,34] Neuropilin 1 (NRP1) co-operates with endothelin and VEGFR-2 in regulating VEGF signal transduction and endothelial cell germination.[35] VEGF elicits phosphorylation of adhesion and dense junction components and increases vascular permeability, leading to increased vascular permeability.[36]

ii) Basic fibroblast growth factor: bFGF is a potent angiogenic factor that promotes endothelial cell growth in vitro and angiogenesis in vivo. bFGF is a known angiogenic factor[37] and a mitogenic factor in a variety of cells, including fibroblasts, smooth muscle cells, and endothelial cells. Tumor size and bFGF levels are negatively correlated. bFGF levels in pleural fluid samples from patients with extensive tumor involvement of the pleural surface have been shown to be significantly lower than those from patients with limited involvement of the pleural surface, who showed significantly higher levels of bFGF and underwent successful pleurectomy.[38] Moreover, bFGF expression is significantly higher in benign pleural effusions than in MPE, and this difference was particularly evident in malignant pleural mesothelioma and benign inflammatory pleural disease.[39]

iii) Heparinase: Heparinase is an endoglycosidase that degrades the extracellular matrix (ECM) and cell surface heparan sulfate, playing an important role in tumor metastasis and angiogenesis.[40] Heparinase-mediated cleavage of heparan sulfate leads to catabolism of ECM and promotes cellular dissemination associated with tumor metastasis, angiogenesis, and inflammation.[41,42] Heparinase is upregulated in almost all human tumors.[43] Heparinase levels are associated with all steps of tumor formation, including tumor initiation, growth, metastasis, and chemotherapy resistance.[44]

Inflammation and Malignant Pleural Fluid

MPE manifests as vascular leakage, leading to pleural space effusion. Its etiology involves not only lymphatic obstruction caused by the tumor but also fulminant inflammation and neovascularization.[21] Chronic inflammation promotes

malignancy development, progression, metastatic spread, and treatment resistance.[7,45] Eosinophils counts are increased in MPE, and these cells promote tumor cell migration and metastasis formation by secreting C-C motif chemokine ligand 6 (CCL6). Furthermore, the inhibition of C-C chemokine receptor 1 (CCR1; a receptor for CCL6), which serves as a receptor for CCL6, has been shown to reduce tumor cell migration and metastasis.[46] Additionally, Kirsten rat sarcoma viral oncogene homolog (KRAS) mutant cancer cells act as molecular determinants that increase propensity of pleural metastatic tumor cells to develop MPE.[47] Nevertheless, the C-C motif chemokine ligand 2 (CCL2) released by pleural tumors plays a pivotal role in the development of MPE by promoting angiogenesis and vascular permeability as well as facilitating the migration of bone marrow-derived cells, including monocytes and mast cells, from the bone marrow to the metastatic environment within the pleura.[6,21,48]

Nuclear factor-κB (NF-κB) activity in tumor cells is critical for MPE formation, drives pro-inflammatory gene expression, and promotes pleural tumor cell survival.[49–51] Mutant cancer cell KRAS is the molecular culprit in MPE formation. KRAS can establish host-to-tumor signaling circuits by promoting IKKα-mediated tumor cell responsiveness to host IL-1β, ultimately leading to inflammatory MPE development and drug resistance.[4] Tumor necrosis factor (TNF)-α is found within the microenvironment of human tumors, including MPE. The MPE model shows host- and tumor-originated TNF-α. Moreover, TNF-α neutralization can remarkably depress tumor proliferation, effusion formation, vascular hyperpermeability, TNF-α and VEGF expression, and angiogenesis, resulting in improved survival.[50,51] For the diagnosis of MPE, the levels of TNF-α and interferon-γ in the pleural fluid are of great practical value.[2]

The mesothelial cells are the major structural axis of inflammation.[52] In response to stimulation by hardeners (eg, talc), mesothelial cells secrete a number of mediators, including IL-8 and monocyte chemotactic protein-1 (MCP-1), VEGF, platelet-derived growth factor (PDGF), bFGF, and TGF-β.[53] These mediators are key players in several inflammatory pathways. IL-8 belongs to the chemokine cytokine family and is associated with the inflammatory process. IL-8 production is notably increased in response to inflammatory stimulation,[54,55] thereby inducing an influx of neutrophils into the pleural space.[56] One study has suggested that IL-8 may be engaged in coagulation events that may result from talc pleurodesis, resulting in early death in patients with MPE.[57] MCP-1 generated by tumor cells is an intrinsic determinant of their ability to provoke MPE formation. MCP-1 appears to have angiogenic and inflammatory properties. Recent studies suggest that MCP-1 may be an effect mediator of NF-κB involved in the inflammatory cascade response in the pathogenesis of MPE.[58] Increased proliferation of tumor cells, evasion of programmed death of tumor cells, sustained formation of neointima, enhanced vascular leakage, and increased macrophage recruitment are possible mechanisms by which MCP-1 promotes MPE.[20,59]

Immune Cells and MPE

Pleural effusion induced by tumor cells establishes its own immune microenvironment during the progression of formation. The tumor microenvironment can be metabolically reprogrammed by immune cells,[60] which reduces immune activation signals and downregulates antigen recognition and presentation. This subsequently induces immunosuppressive effects within MPE environment,[61] thereby facilitating the growth of disseminated tumor cells and promoting immune escape in MPE. Various immune cell populations within tumor microenvironment of malignant pleural effusion, including T lymphocyte subsets, tumor-associated macrophages, dendritic cells, natural killer cells, myeloid-derived suppressor cells, and B lymphocytes are subject to immunosuppressive effects mediated by MPE. Consequently, this facilitates the unrestricted growth of tumor cells in MPE that have evaded immune surveillance.[62] Complex interactions between immune cells are essential in the pathogenesis of MPE. Single-cell analysis of multiple immunophenotypes of MPE have shown that immune cells in MPE are enriched for transcriptional signatures of macrophages, dendritic cells, B cells, and functional T cells.[63] Th17 cells and their cytokines are important elements in many diseases, especially MPE. MPE is mediated by the activation of Th17 cells and their interactions with other immune cells. In addition, Th17 cells and their pro-differentiation cytokines have been proposed to be recruited into the development of MPE by mediating tumor-promoting and anti-tumor functions, and modulating the production and differentiation of Th17 cells in MPE.[64]

As the main immune cells in the cancer microenvironment, tumor-associated macrophages represent the major inflammatory cells in MPE, and the M2 macrophage number can reflect poor prognoses in these patients.[65] Tumor-associated macrophages represent the predominant inflammatory cell population in MPE, with M2 polarization being

induced by signaling through the colony-stimulating factor 1 (CSF1)/CSF1 receptor (CSF1R) axis. CSF1R+ macrophages facilitate the onset of PE by increasing vessel perfusion, destabilizing the vasculature, and/or fostering an immunosuppressive environment.[65] Macrophages in malignant ascites and MPE can transform into fibroblastic-like elements.[66] The results of single-cell RNA-sequencing analyses shed light on the immune-related milieu of MPE with small cell lung cancer (SCLC). B cells and T cells exhibit varying degrees of expression of tumor-associated genes pertinent to SCLC during the differentiation process of MPE. Furthermore, immune cells are primarily involved in the communication with malignant cells by means of major histocompatibility complex II (MHCII), IL-16, lectin, and amyloid precursor protein pathways.[67]

Tumor-Associated Fibroblasts and MPE

The presence of MPE is indicative of advanced cancer and is associated with a poor prognosis that develops because of complex orchestrated interactions among tumor cells, inflammatory cells, as well as the vasculature. Studies of the cancer and stromal cell secretome have provided valuable insights into the interactions of cells in the malignant environment as well as the crucial role of critical target effectors in the creation of premetastatic sites at remote metastatic locations.[68] Cancer-associated fibroblasts represent crucial stromal constituents in primary and diffuse pleural lesions.[69] During tumorigenesis, the imbalance of cell homeostasis and the high heterogeneity of cancer-associated fibroblasts have major effects on the protein pool secreted by malignant tumor cells.[70]

Adenocarcinoma (AdC), which is often accompanied by PE, is the most prevalent subtype of carcinoma. Lumican is a sulfated kitin that belongs to the SLRP group of ECM proteins and is expressed in various forms in a wide range of organs and tissues, including skin, corneas, bones, arteries, kidneys, and lungs. Alterations in lumican expression are thought to be associated with the spread of cancer.[71,72] The study by Cappellesso et al,[73] showed that in AdC surgical specimens, lumican expression was lower within cancer cells and higher and more diffuse throughout the matrix surrounding the neoplastic tumor. Western blot analysis indicated that the high fluorescein values of AdC PEs may have been released by fibroblasts surrounding the tumor. PDGF levels in PEs from lung adenocarcinoma are significantly greater than that those in PEs associated with SCLC and non-malignant conditions, and this finding correlates with fibroblast proliferation and pro-activity.[74]

Hypoxia-Inducible Factor and MPE

Repeated MPE caused by NSCLC is difficult to cure with regular therapy. In an extensive MPE cohort study, patients with recurrent MPE showed significantly increased Claudin-4 (CLDN4) expression in PE cells and poorer overall survival.[75] CLDN4 expression is associated with hypoxia-inducible factor 1-α (HIF1-α) and VEGF-A. The HIF1-α (P) and CD133/HIF1-α (S) ratios have been shown to be markers for the assessment of lymph node metastasis in patients with MPE.[76]

Water Channel Protein and MPE

Increased vascular permeability in the chest wall and an imbalance in the production and absorption of pleural liquid in patients with lung cancer may be the principal cause of the emergence of MPE. Several studies have implicated aquaporin-1 (AQP1) in this pathological mechanism.[77,78] Aquaporins (AQPs) are a family of transmembrane-bound proteins that facilitate transmembrane and transseptal permeability across cellular membranes, playing a crucial role in water transport and metabolic processes in vivo.[79] Among the six aquaporins identified in the lungs, AQP1 has been most comprehensively studied.[80–82] AQP1 is exposed on the sural surface of the visual and parietal pleura. It plays a critical role in pulmonary edema and severe lung damage, since AQP1 deficiency leads to impaired fluid exchange between pulmonary capillaries and interstitial tissue. PE is mainly absorbed by the lymph vessels in the upper parietal pleura. The fundamental function of AQP1 is regulation of fluid homeostasis within the thoracic cavity. Research involving AQP1-knockout mice demonstrated that the time required for osmotic pressure in the pleural cavity to achieve equilibrium was significantly longer than that in wild-type mice. In vitro investigations have indicated that inhibition of AQP1 can influence the osmotic pressure associated with pleural fluid transport.[77,78]

These studies underscore the critical role of AQP1 in maintaining pleural fluid homeostasis. Furthermore, AQP1 has been implicated in tumorigenesis, with evidence indicating that this protein is significantly overexpressed in various malignancies, including lung cancer.[83,84] Inhibition of AQP1 has been demonstrated to impede the invasion and progression of various tumors, while quantitative transcriptome analysis of AQPs showed that increased transcript ratios of AQP1, AQP3, AQP5, and AQP9 were associated with poor survival.[85,86] Increased levels of AQP1 mRNA as well as VEGF expression have also been shown to be correlated with elevated MPE volumes.[87]

Advancements in the Application of TCM for the Management of MPE

PE is not simply a byproduct of malignancy, but also an energetic driver of tumor growth, necessitating changes in the treatment paradigm of MPE to aggressively control PE formation. These changes are vital to lengthen patients' survival and enhance their quality of life. At present, the management of MPE in Western medicine is primarily based on symptomatic treatment and palliative care, which can still achieve some efficacy in the early stages. For large or rapidly recurring PEs, only puncture aspiration is possible, but repeated maneuvers can cause disturbances in water and electrolyte balance and protein loss and may also increase the danger of pleural infection.

Combinations of Chinese and Western medicine have been widely recognized for treating MPE. TCM treatment can boost the immune system, alleviate complaints, and increase the quality of life with fewer adverse reactions, making the treatment more acceptable to patients. This approach is the preferred option for patients who cannot tolerate chemotherapy.[88–90] Numerous clinical trials have shown favorable efficacy of this approach.[91,92]

1) Formulas: Formulas are prescriptions for combinations of plants/minerals used by TCM practitioners based on their clinical experience to enhance therapeutic efficacy and minimize adverse effects. TCM practitioners use formulas containing multiple herbs to harmonize their effects and restore the patient's "balance".[93]

i) Gansuigancao Tang: Gansuigancao Tang (GSGCT) is a TCM soup that consists of two herbs, Gansui and Gancao, and is uniquely effective in the treatment of edema. Among the two constituent herbs, Gansui promotes urinary excretion and is prescribed in cases of swelling, abdominal ascites, and asthma. Gansui has also shown diuretic effects and has been reported to drain MPE ($P < 0.01$).[94] Gansui has a therapeutic effect on MPE, and combining it with licorice can diminish its efficacy and even produce severe toxicity in certain proportions. Gansui:Gancao at a ratio of 2:1–1:1 is considered a dose-toxicity-efficacy inflection point. At ratios within this point, GSGCT has a curative therapeutic effect on MPE with minimal toxicity. However, at ratios higher than this point, GSGCT can cause liver and cardiac toxicity, which is detrimental to the efficacy of the treatment.

ii) Xiaoshui decoction: Xiaoshui decoction (XSD) is a herbal compound adapted from the classic formula for the treatment of "Hanging Drinks" in The Essentials of the Golden Poverty-Tinglidazaoxiefei Decoction. XSD is often utilized in MPE management. XSD has shown efficacy in cleaning the lungs and removing phlegm, facilitating horizontal wheezing, and reducing the retention of fluid. One study[95] showed that XSD effectively inhibited the evolution of MPE through decreased pleural leakage and angle formation and reprogramming the tumor-associated macrophage phenotype by inducing autophagy.

iii) Shizao tang: Shizao tang (SZT), which is used for the treatment of typhoid fever, is composed of Coriander, *Glycyrrhiza glabra*, Dacryocybe, and Jujubae. SZT is prescribed for the healing of edema, ascites, pleural effusions, and other disorders where fluid balance is impaired. *Euphorbia kansui* and *Euphorbia pekinensis* have been found to have diuretic and laxative effects on improving water retention in rats with malignant ascites.[96] The results of network pharmacological analysis suggested that SZT limited MPE by modulating the VEGF-phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT) signaling pathway and altering vascular permeability and through modulation of the PI3K-Akt /MAPK/NF-κB pathway by upregulating AQP8 protein production. In animal studies, SZT/VSZT significantly reduced PE, increased urinary output, decreased inflammatory cytokine expression, and elevated AQP8 levels ($P < 0.05$).[97]

iv) Ginseng and Astragalus Decoction: Ginseng and Astragalus Decoction (GAD) has been reported to help replenish Qi and Yang.[98] GAD was recorded to be used in Ge Hong's Elbow Preparedness Formula of the Eastern Jin Dynasty, and subsequently appeared in classic formulas for the treatment of water disorders, including Baoyuan Tang, Buzhongyiqi Tang and Guizhi Tang. Recent studies in modern pharmacology have shown that astragalus and ginseng have anti-tumor and immunological actions. One study utilized network pharmacology and molecular-docking technology to explore the

potential compounds and activities of GAD for the treatment of MPE. The target core network included 22 key compounds, 26 main targets, and 16 signal paths of GAD. Molecular-docking analyses revealed six partial docking targets to ginsenoside RH2, kaempferol, mangostin, fructone A, and quercetin. Multiple C-components of GAD targeting signaling pathways are useful for treating MPE.[99]

Purification

i) Kanglaite injection: The major component of Kanglaite injection (KLT) is Coix seed oil, which is emulsified by modern technology. KLT, which is recognized as a broad-spectrum anticancer agent, has been employed in China for the treatment of malignant tumors.[100] One study[101] reported that KLT administered at a dosage of 200 mL/day for 21 consecutive days resulted in a remarkable increase of 55.9% in the mean body weight of patients with advanced lung cancer in comparison with their pre-treatment weight. KLT has been shown to increase anti-tumor activity in clinical trials, improving patients' quality of life and reducing side effects.[102,103] KLT combined with conventional chemotherapeutic agents has shown superior efficacy and safety in controlling MPE in comparison with intrapleural injection of conventional chemotherapeutic agents alone.[92]

ii) Aidi injection: Aidi injection consists of xanthoxylin, ginsenoside, astragaloside, and artemisinin saponin E.[104] As an important adjuvant for chemotherapy, Aidi injection is frequently used in conjunction with gemcitabine and cisplatin to manage MPE in NSCLC. Research has demonstrated that the clinical effectiveness of Aidi injection alone administered into the pleural cavity is comparable to that of cisplatin. The combination of Aidi injection and cisplatin has been shown to substantially enhance patients' complete remission rates and quality of life while demonstrating a reduction in pleural fixation breakdown, disease evolution, and secondary events. For moderate-to-severe bruises, the combination of Aidi injection and cisplatin has been shown to significantly enhance clinical symptoms as well as improve Karnofsky performance status scores by ≥50 or the expected survival duration by ≥3 months. Evidence indicates that Aidi injection can perform a major clinical function in the management of MPE.[105]

iii) Elemene injection: β-Elemene extracted from a species of ginger is processed into elemene injection (EI),[106] which has been widely used as an adjuvant anti-tumor drug in numerous countries.[107] The use of EI alone has been found to significantly improve the objective response rate (ORR) in MPE and reduce the rate of bladder cancer recurrence, while also resulting in fewer adverse reactions. EI is emerging as an efficacious proprietary drug to treat MPE with non-inferior efficacy and less toxicity than conventional drugs.[108]

External Medicines

Over the past few years, TCM-based external medicines have played an essential part in MPE treatment due to their distinctive benefits.[88] Glauberite is a commonly used Chinese medicine, and its main component is sodium sulfate ($Na_2SO_4 \cdot 10H_2O$). Glauberite can osmotically soak up the effusion to help remove edema. When applied externally to the chest, glauberite can create a local hyperosmotic state and stimulate the absorption of excess effusion through osmotic pressure. Mirabilite is used to treat many clinical conditions, including inflammation and edema; it has also been used for wound healing and intestinal preparation before microscopic examination.[109] Rhubarb has been shown to clear heat and detoxify inflammation.[110] Rhubarb has the potential to cleanse the intestines, alleviate internal abdominal pressure, mitigate endotoxin-induced intestinal mucosal damage, decrease pancreatic amylase secretion, resolve inflammatory edema, and reduce serum levels of IL-6.[111] The synergistic action of mirabilite and rhubarb can relieve congestion and reduce swelling. Topical application of glauberite and rhubarb, in conjunction with thoracic perfusion of cisplatin, has been shown to be an effective approach for treating MPE. The underlying mechanism of this combined treatment may involve the reduction of capillary permeability, enhancement of microcirculation barriers, facilitation of a hypertonic state, and osmotic suction of fluid in the chest pleura, thereby promoting resolution of MPE.[112]

Conclusions

The presence of MPE often indicates severe disease, with the rapid accumulation of PE mechanically restricting lung expansion and causing considerable damage to the patient's respiratory and circulatory systems. In Western medicine, symptomatic management and palliative care are frequently employed for the treatment of MPE. Enhancing symptom management,

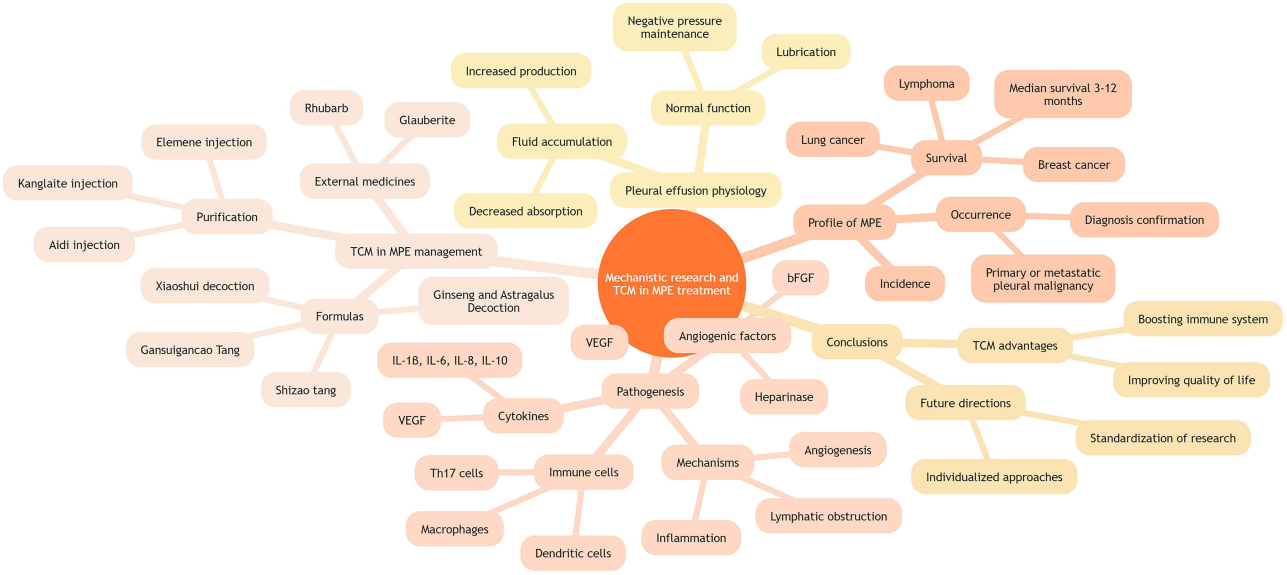

Figure 1 A Mermaid mind map representation of the mechanistic research and traditional Chinese medicine (TCM) in the treatment of malignant pleural effusion (MPE).

improving quality of life, and extending survival are the primary goals of MPE treatment. TCM has demonstrated distinctive advantages in achieving these goals. The combination of TCM and Western medicine represents a notable trend in advancing MPE treatment. The integration of local medicine with internal administration of TCM has demonstrated a notable auxiliary therapeutic effect. Treatment protocols should prioritize individualized approaches tailored to the patient characteristics and stages of illness.

Currently, the research level of TCM regarding MPE requires enhancement. The diagnostic and therapeutic criteria, research methodologies, and statistical analyses of results require further standardization to bolster the credibility of these scientific results (Figure 1).

Abbreviations

AQP1, aquaporin-1; bFGF, basic fibroblast growth factor; CLDN4, claudin-4; CSF1R, CSF1 receptor; KLT, kanglaite injection; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemotactic protein-1; MPE, malignant pleural effusion; NRP1, neuropilin 1; NSCLC, non-small cell lung cancer; ORR, objective response rate; PDGF, platelet-derived growth factor; PE, pleural effusion; TCM, traditional Chinese medicine; TGF-β1, transforming growth factor-β1; TGF-β, transforming growth factor β; Th17, T helper cell 17; VEGF, vascular endothelial growth factor; VSZT, toxic members in shizaotang processed with vinegar.

Data Sharing Statement

No additional data are available.

Ethics Approval

The study did not require ethical review board approval or informed consent.

Use of AI

The authors declare that they have not use AI-generated work in this manuscript.

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Disclosure

All authors declare that they have no competing interests.

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