Advances and limitations in the treatment of pleural mesothelioma - a review of the current state of knowledge

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Abstract

Pleural mesothelioma is an aggressive cancer with a strong association to asbestos exposure, characterized by late diagnosis, limited treatment options, and dismal prognosis. Despite advances in multimodal therapy, the median survival rarely exceeds 18 months, underscoring the need for more effective strategies.

Current standard treatments include platinum-based chemotherapy (cisplatin/pemetrexed) and, for select patients, radical surgery (pleurectomy-decortication or extrapleural pneumonectomy), though the latter remains controversial due to high morbidity and lack of clear survival benefit. Immunotherapy, particularly dual checkpoint inhibition (nivolumab/ipilimumab), has emerged as a first-line option for non-epithelioid MPM, demonstrating improved survival in the CheckMate 743 trial. However, response rates remain modest, and resistance mechanisms are poorly understood.

Emerging therapies target molecular alterations, such as *BAP1* and *CDKN2A* mutations, with PARP and CDK4/6 inhibitors showing early promise. Biomarker research, including mesothelin and Fibulin-3, aims to refine diagnostics and prognostication, though none are yet validated for routine use. Palliative interventions, such as talc pleurodesis and radiotherapy, play a key role in symptom control.

Future directions include novel immunotherapies (bispecific antibodies, CAR-T cells), oncolytic viruses, and personalized approaches guided by genomic profiling. Collaborative efforts to expand clinical trials are critical, given MPM's rarity and heterogeneity. While progress is incremental, integrating systemic, local, and supportive therapies offers hope for improving outcomes in this challenging disease.

Keywords: pleural mesothelioma, pleural tumors, asbestos, immunotherapy, biomarkers

Introduction

Pleural mesothelioma is a rare, malignant tumor originating from the mesothelial cells of the pleura [1-4]. Its main cause is exposure to asbestos, and the long latency period means that the disease is often diagnosed at an advanced stage, which significantly limits the possibilities of effective treatment [1-4].

Pleural mesothelioma is characterized by an extremely aggressive clinical course, rapid local spread, and resistance to many conventional treatment methods [2,4]. The histopathological classification distinguishes three main subtypes of the tumor: epithelial, sarcomatous, and mixed (biphasic), the first of which has the best prognosis [2,5]. Due to nonspecific symptoms, such as dyspnea, chest pain, and weight loss, diagnosis often occurs at an advanced stage of the disease, which additionally limits the therapeutic options [2].

Over the past two decades, significant progress has been made in the diagnosis and treatment of mesothelioma. Modern imaging techniques, thoracoscopy-assisted biopsies, the development of molecular tumor markers, and advances in surgery, radiotherapy, and clinical oncology have introduced new treatment options. Particular hopes are currently associated with immunotherapy (e.g., checkpoint inhibitors), molecularly targeted therapies, and combination (multimodal) treatment combining different therapeutic approaches [2,4,5].

Despite these achievements, the treatment of pleural mesothelioma still encounters numerous barriers. These include limited efficacy of classical chemotherapy, lack of clear criteria for surgical qualification, high risk of relapse, and difficulties in conducting clinical trials due to the rarity of the disease and its varied course [5].

The aim of this review article is to comprehensively analyze the current state of knowledge on the treatment of pleural mesothelioma. The latest advances in therapy, results of clinical trials, controversies regarding the procedure, and prospects for the development of new treatment

strategies will be discussed. Particular attention was paid to both the benefits and limitations of available methods in the context of personalizing treatment and improving patient prognosis.

Epidemiology and risk factors

Mesothelioma is a rare malignant tumor, accounting for approximately 80–90% of all mesothelioma cases. Its global incidence remains relatively low, with an estimated annual incidence of 1–2 cases per million in the general population. It is more common in men than women [1-3].

The primary and best-known risk factor for mesothelioma is exposure to asbestos fibers, which are inhaled and can become embedded in the pleural lining, causing chronic inflammation, cell damage, and carcinogenesis [1,2].

Although asbestos exposure is the predominant risk factor, not all individuals exposed to asbestos develop mesothelioma, suggesting a multifactorial etiology. Other proposed risk factors include genetic susceptibility, including mutations in the BAP1, CDKN2A genes, exposure to other fibrous minerals such as erionite, prior chest radiotherapy, and chronic pleurisy [1-5].

Pathogenesis

The pathogenesis of pleural mesothelioma involves a complex interplay of environmental exposures, genetic alterations, and chronic inflammatory processes that drive malignant transformation of mesothelial cells.

Exposure to asbestos plays a significant role in many mesothelioma cases, and the link between asbestos and the disease is well recognized. Among men in Western countries, asbestos is the leading cause of mesothelioma, whereas its role in causing the disease in women is less frequent [3,6,7]. Asbestos refers to a group of hydrated silicate minerals with similar physical properties, divided into two main groups-amphiboles, which include amosite, crocidolite (the most carcinogenic type), tremolite (blue asbestos), actinolite (brown asbestos), and anthophyllite- and serpentines, represented solely by chrysotile (white asbestos), the most commonly used but less carcinogenic form [1,3,8-10]. Fibers of crocidolite that are particularly thin and extended-specifically those over 8.0 μm long and wider than 0.25 μm-are considered especially hazardous due to their prolonged retention in the pleura and their ability to infiltrate lung tissue,

causing chronic injury and localized inflammation [1,8]. Asbestos fibers inflict both mechanical and oxidative harm on cells while also promoting a proinflammatory setting and drawing in substances and proteins that may contribute to carcinogenesis [3]. Exposure to asbestos results in DNA damage through the action of reactive oxygen and nitrogen species, as well as chronic inflammation induced by immune cells, primarily macrophages and mast cells. Macrophages phagocytose asbestos fibers, release TNF-α, and stimulate mesothelial cells to express the TNF-α receptor, which activates the NF-κB pathway-promoting the survival of damaged cells and the accumulation of mutations. Mast cells contribute similarly, particularly in response to crocidolite, by releasing TNF-α and stimulating NF-κB activity through autocrine and paracrine signaling. These ongoing inflammatory and oxidative processes foster a microenvironment that promotes the malignant transformation of mesothelial cells into pleural mesothelioma [1,3,8,11-14].

As far as genetic mutations are concerned, the primary mutation associated with pleural mesothelioma is a germline alteration in the BAP1 (BRCA1-associated protein 1) tumor suppressor gene [15]. BAP1, a deubiquitinase enzyme involved in BRCA1-associated DNA repair complexes, plays a key role in regulating cell cycle progression, DNA repair, chromatin remodeling, and cell differentiation. Its tumor-suppressive function is linked to reduced tumor growth and inhibition of apoptosis under metabolic stress [1,8,16]. Interestingly, several germline mutations, particularly those affecting DNA repair pathways, have been shown to reduce the level of asbestos exposure necessary to trigger the development of mesothelioma [3,17]. The identification of BAP1 as a key regulator of metabolism and cell death has advanced understanding of asbestos-related carcinogenic mechanisms. Further research is needed to clarify the role of mesothelioma-predisposing genes in these molecular pathways [18,19].

Classification - histopathological subtypes

As outlined in the 5th edition of the WHO classification (2021), primary malignant pleural disease includes the following subtypes: epithelioid, sarcomatoid, biphasic mesothelioma, localized and diffuse mesothelioma [2,20-22]. Additionally, this classification has also introduced mesothelioma in situ (MIS) [20-22]. In many cases, a mixture of epithelioid and sarcomatoid histologies is present [1]. The variety of histological patterns seen in mesotheliomas makes diagnosis based solely on morphology challenging. Thus, the use of

immunohistochemical techniques (IHC) is suggested to aid diagnosis. Detailed information regarding the specific features of each subtype is compiled in Table 1. Beyond this classification, the TNM (Tumor, Node, Metastasis) system is also employed, particularly in the context of treatment planning [15].

Table 1. Pleural Mesothelioma: Subtypes and Characteristics [1-4,20-24]

Subtypes	**Characteristics**
Histopathological subtype–based classification	
Epithelioid mesothelioma	- highest occurrence - structural heterogeneity - associated with favorable prognosis - diagnostic uncertainty when compared to other tumor types - loss of BAP1 expression and CDKN2A deletion in up to 70% cases
Sarcomatoid mesothelioma	- identifiable by their spindle-shaped cells, grouped in fascicular or disorganized patterns, extending into adipose tissue or/and lung tissue - tend to have a worse clinical outcome - cells demonstrate a range of abnormalities and may include various tissue forms - more frequently observed loss of CDKN2A - Desmoplastic mesothelioma - subtype of sarcomatoid mesothelioma
Biphasic mesothelioma	- both sarcomatoid and epithelioid elements must constitute at least 10% of the tumor - tend to have a worse clinical outcome
Disease distribution–based classification	
Mesothelioma in situ (MIS)	- an early-stage tumor arising from mesothelial cells - a monolayer of atypical cells on the pleural surface, lacking infiltration into deeper layers - difficult to identify using only microscopic appearance
Localized pleural mesothelioma (LPM)	- presents as a single mass confined to a specific pleural area - less invasive form than DPM - surgical resection is feasible in some cases
Diffuse pleural mesothelioma (DPM)	- diffuse and expansive type - severely invasive malignant growth

	- more common form than LPM

Symptoms

The onset of mesothelioma symptoms can be delayed for 10 to 50 years after asbestos exposure, reflecting the extended time this disease takes to develop [1,8,25]. Peritoneal mesothelioma often presents with nonspecific symptoms such as shortness of breath caused by pleural effusion, which occurs in about 90% of patients, chest pain, fatigue, dry cough, as well as unintended weight loss and reduced appetite [1,4,8,21,25]. Dyspnea is the primary symptom that prompts patients with pleural mesothelioma to seek medical attention, while fever and night sweats are less frequently reported. Patients who develop ascites as a secondary manifestation of pleural mesothelioma may experience a feeling of fullness after eating small amounts and discomfort or reluctance when trying to lean forward. As the disease advances, growing pressure on the mediastinum and restricted lung function lead to worsening shortness of breath and a persistent dry cough. Ensuring proper nutritional care and performing pleural fluid drainage can significantly ease patient discomfort [18].

Diagnosis

Imaging tests

If a physical exam indicates the presence of pleural effusion, an initial step typically involves ordering a chest X-ray, a computed tomography scan (CT) and magnetic resonance [18,26]. For the detection of pleural mesothelioma, chest radiography serves as the first diagnostic imaging method. The International Mesothelioma Interest Group (iMIG) Pleural Imaging Expert Panel recommends capturing both anteroposterior and lateral chest images, with careful attention to include the anterior and posterior costophrenic angles [26,27]. Pleural plaques, thickened connective tissue on the parietal pleura that may calcify, are the most common sign of long-term asbestos exposure, seen in about 20% of cases. Because radiographic findings are often nonspecific and vary by disease stage, advanced imaging is needed to accurately assess and differentiate pleural mesothelioma [26-28]. Conventional chest radiographs are limited in their ability to diagnose and stage mesothelioma, as substantial pleural fluid can conceal pleural or thoracic abnormalities and prevent the visualization of small cancerous lesions [21]. Multidetector computed tomography (CT) is essential for morphologic evaluation, staging, and treatment planning of pleural mesothelioma offering rapid, high-resolution images that clearly

show thoracic and abdominal anatomy in any plane [26,29]. Because pleural mesothelioma exhibits a complex, multiplanar growth with fragmented, irregularly shaped lesions across multiple CT slices, the iMIG Pleural Imaging Expert Panel recommends evaluating multidetector CT scans in three high-resolution planes—usually 1–2 mm slices for axial views and 2–3 mm for sagittal and coronal views [26,30]. The scan should cover the entire chest, extending caudally to the level of L3 to include the posterior costophrenic angles. Intravenous iodinated contrast should always be used—unless contraindicated—as it significantly enhances CT detection and quantification of PM, with a recommended scan delay of 50–60 seconds after injection [26,27]. Contrast-enhanced CT is useful for evaluating the local extent of pleural mesothelioma, as it can reveal infiltration into the pericardium, mediastinum, trachea, esophagus, and chest wall, as well as tumor extension across the diaphragm into abdominal structures [26].

Since magnetic resonance imaging (MRI) offers superior soft tissue contrast compared to computed tomography (CT), it is occasionally used for staging purposes. MRI is more sensitive in detecting invasion of the diaphragm, chest wall, and cardiovascular structures [18,26]. It is also helpful in distinguishing between malignant and benign pleural abnormalities [26]. MRI is rarely used in diagnosing and staging pleural mesothelioma because of its high cost, limited accessibility, and long scan durations. What is more, a key limitation of MRI image quality is the presence of artifacts—such as susceptibility or motion-related issues. Accurate detection of subtle findings relies on clear visualization of the pleura and surrounding structures, making effective motion artifact reduction essential for a reliable diagnosis [18,26].

Invasive tests

In the diagnosis of MPM, the use of invasive methods is necessary to make a final diagnosis and is crucial in planning further treatment [1,4]. Imaging studies may not provide sufficient sensitivity and specificity to make an accurate diagnosis. Large pleural effusions may mask small lesions that will become undetectable with noninvasive imaging methods [21]. In order to precisely determine the stage of the disease and the type of tumor at the cellular level, it is advisable to perform specialized invasive tests. Among others, such as thoracoscopy, open pleural biopsy, fine-needle biopsy or the use of bronchoscopy to assess the mediastinum [1]. Fine-needle biopsy is not commonly performed due to its low sensitivity [4]. In cases where thoracoscopy is contraindicated or cannot be performed, alternatives include computed

tomography (CT) or ultrasonography (US)-guided biopsy [21]. In the initial evaluation of pleural mesothelioma, US-guided thoracentesis is recommended to collect pleural fluid for cytological testing. This procedure is not particularly sensitive diagnostically. The examination confirms the disease in only one third of cases. Thoracocentesis also plays an important role in relieving symptoms. Reducing the amount of fluid in the pleural cavity can improve the patient's comfort by reducing shortness of breath and the feeling of tension in the chest [1,4,21]. Thoracoscopy can be performed on the patient in several ways. It is performed in the form of pleuroscopy or in the form of video-assisted thoracic surgery (VATS) [21]. VATS is the gold standard for diagnosis, it allows for precise collection of samples from at least 3 different areas, and during the examination therapeutic procedures can also be performed [18]. Histopathological analysis plays an important role. It allows for differentiation of the type of mesothelioma. However, establishing a clear diagnosis of mesothelial changes is a great challenge. Especially when it is necessary to differentiate malignant neoplasm from benign changes, such as fibrous pleurisy or reactive mesothelial hyperplasia [1]. An important test is immunohistochemistry. It allows for more accurate differentiation of pleural mesothelioma from sarcoma [4]. A large number of immunohistochemical markers are needed to diagnose malignant pleural mesothelioma [1]. Unfortunately, even the use of highly sensitive methods, such as IHC, does not exclude misdiagnosis. A less frequently used invasive test is diagnostic laparoscopy, which can be used when there is a suspicion of metastases in the abdominal cavity [4]. In summary, invasive tests are crucial in the diagnosis of MPM, because even pleura that appears unchanged should be routinely assessed, and biopsies must reach deep enough to allow for the assessment of invasion of the chest wall tissues [18].

Biomarkers

Biomarkers are used in detailed diagnostics and in determining the prognosis of cancers. Due to the lack of appropriately sensitive and specific diagnostic tests, the identification of biomarkers remains the subject of intensive research [31-33]. In the diagnosis of MPM, biomarkers tested in blood serum and pleural fluid are not appropriately sensitive and specific. Currently, the most important marker is mesothelin (SMRP). It is detected in both pleural fluid and serum. J is a glycoprotein that is located on the surface of pleural mesothelioma cells. It is characterized by high specificity of about 100% in both blood and pleura, unfortunately its sensitivity remains limited [1,31,33]. Other markers taken from blood in the diagnosis of MPM

are: Fibulin 3, which is also found in the pleura, osteopontin and megakaryocyte potentiating factor. High levels of Fibulin 3 may indicate a more severe, more advanced stage of the disease [1]. Medical articles also contain information about markers such as: cytokeratin fragments CYFRA 21-1 and hyaluronic acid. They can be detected in pleural fluid. CYFRA 21-1 may be helpful in differentiating malignant and benign pleural lesions. Hyaluronic acid, on the other hand, is highly specific. Despite the constant search for markers and their promising results, there is still a lack of evidence that would indicate improved treatment outcomes due to earlier detection of the disease. The development of proteomics techniques and combining molecular data with clinical examination and imaging studies are essential to achieve real progress in the future in the diagnosis of pleural mesothelioma [31]. In the meta-analysis by Zhu et al. (2023), 46 studies were analyzed that determined the diagnostic value of biomarkers, both single and in various combinations. As a single marker, Fibulin-3 achieved the highest sensitivity and specificity among single markers. On the other hand, the combination of biomarkers in diagnostics resulted in a greater increase in its value. The best results were obtained for the combination of MTAP + Fibulin-3 (Sensitivity 81%, specificity 95%). Another important clue is the information that high MTAP expression is associated with prolonged survival, which allows the use of this marker in determining prognosis. The study proved that combining markers in combinations allows the use of their diverse mechanisms. They are becoming more important in the diagnostic process than individually determined biomarkers. In the future, it is worth expanding clinical studies in this direction [32].

Treatment

Surgical treatment

Surgical intervention is generally reserved for a limited number of mesothelioma patients, as the procedure is highly invasive and associated with significant risks, even in those who appear to be in good health and have tumors with favorable features. Before considering surgery, a pleuroscopic evaluation is often necessary to determine whether the operation is both appropriate and technically possible. However, clinical research, randomized phase 3 trial MARS2, has shown that surgery does not provide a clear survival advantage over chemotherapy alone. Despite this, there may still be select patients for whom surgery could offer meaningful, individualized benefit [34].

The surgical management of pleural mesothelioma requires thorough preoperative staging using imaging studies, ideally complemented by mediastinoscopy or endobronchial ultrasound. Careful selection of patients is also essential—only those with adequate overall health and cardiopulmonary reserve who can tolerate potential extrapleural pneumonectomy (EPP) should be considered. The primary goal of surgical treatment remains macroscopic complete resection of the tumor, which in practice often corresponds to an R1 resection (i.e., with microscopic residual disease at the margins) [35]. Surgical treatment options for malignant pleural mesothelioma vary in scope and invasiveness. These range from limited procedures, such as partial pleurectomy—where only selected areas of diseased pleura are removed—to more extensive surgeries, including pleurectomy-decortication (removal of both the parietal and visceral pleura along with any tumor-involved lung tissue), extended pleurectomy-decortication (which also includes resection of the pericardium and diaphragm when affected), and the most aggressive approach, extrapleural pneumonectomy (involving removal of an entire lung along with the pleura, diaphragm, and pericardium, with the intent to eliminate all visible disease). Despite its radical nature, extrapleural pneumonectomy has shown limited long-term benefit, with five-year survival rates around 14% and a median survival of approximately a year and a half. Moreover, a randomized study comparing this procedure followed by radiotherapy to a non-surgical approach (both alongside standard chemotherapy) found that patients who underwent surgery had shorter overall survival and experienced a significantly higher rate of serious complications. These included cardiopulmonary issues, infections, the need for reoperations, and in some cases, treatment-related death. However, the validity of these results has been questioned due to high dropout rates and differences in disease biology between the groups, which may have influenced outcomes. On the less invasive end, partial pleurectomy has also not demonstrated a clear survival benefit. In fact, patients undergoing this procedure had slightly worse one-year survival compared to those who received talc pleurodesis, along with a higher rate of complications and longer hospital stays [36]. Additional innovative approaches, which are only beginning to be reported, include induction therapy with dual immune checkpoint inhibitors followed by tumor resection. Preliminary data regarding the tumor microenvironment and treatment response are intriguing (study NCT02592551) [35].

Chemotherapy

Chemotherapy remains a fundamental component in the treatment of malignant pleural mesothelioma (MPM), particularly in cases where the tumor is not suitable for surgical resection due to advanced stage or unfavorable anatomical characteristics. In such situations, systemic treatment can provide substantial relief from symptoms, enhance quality of life, and potentially extend survival. Various chemotherapy protocols are utilized, with the combination of cisplatin and pemetrexed being the most widely adopted. This regimen has demonstrated greater efficacy than cisplatin alone in terms of overall survival, duration of disease control, and tumor response rates. Moreover, patients receiving this combination tend to experience reduced symptom burden and better quality of life when compared to those managed solely with supportive care. In some studies, the addition of bevacizumab to cisplatin-pemetrexed therapy—forming a triplet regimen—has been associated with further improvements in progression-free and overall survival. However, the available evidence remains limited, and no formal recommendations have been established. Nevertheless, this strategy may be considered for select patients without contraindications to antiangiogenic therapy. For those responding well to chemotherapy or with stable disease, the standard approach involves 4 to 6 treatment cycles, followed by a treatment-free interval. In certain cases, the same regimen can be reintroduced as second-line therapy, provided the patient previously tolerated it well. In individuals who are unsuitable for cisplatin, carboplatin may be used as an alternative with comparable clinical outcomes and potentially lower toxicity. Beyond survival benefit, chemotherapy also plays a key role in alleviating major symptoms such as pain and breathlessness, leading to improved daily functioning. In patients with good performance status (≤2 on standard scales), first-line treatment with platinum-based agents combined with pemetrexed—supported by vitamin B12 and folic acid supplementation to minimize adverse effects—has proven effective. While side effects such as nausea, leukopenia, and severe neutropenia may occur, the benefits typically outweigh the risks. Compared with single-agent cisplatin, this combination leads to higher response rates, longer survival, and more durable disease control. The average number of treatment cycles administered in these regimens is six. Alternative therapeutic strategies are also being explored in clinical trials. For patients with compromised general health (performance status ≥2), monotherapy options such as pemetrexed, vinorelbine, or gemcitabine may be appropriate. In those with poor performance status (≥3), the primary goal shifts to symptom management through palliative care.

If initial pemetrexed-based chemotherapy results in disease control and further treatment is warranted, reusing the same regimen as a second-line option may be viable. Outside of clinical trial settings, vinorelbine is another possible alternative. In carefully selected patients with epithelioid histology and no symptoms, a strategy of active surveillance and close monitoring may be appropriate before initiating systemic therapy. Nevertheless, some research has indicated that early initiation of chemotherapy can improve survival outcomes and extend the period of symptom control [4].

Radiotherapy

In select cases, radiation therapy—either before (neoadjuvant) or after (adjuvant) surgery—may be considered for patients scheduled to undergo extrapleural pneumonectomy (EPP). Ideally, such treatments should be administered within clinical trials conducted at highly specialized centers.

Evidence from clinical studies, such as the IMPRINT trial, has highlighted the potential benefits of combining chemotherapy, pleurectomy/decortication (P/D), and targeted radiotherapy like hemithoracic intensity-modulated radiation therapy (IMRT). In particular, individuals with resectable epithelioid mesothelioma may experience clinical benefit from an approach that includes accelerated hemithoracic IMRT followed by EPP.

Modern radiation technologies—such as IMRT and three-dimensional conformal radiation therapy (3D CRT)—allow precise targeting of cancerous tissues, helping to deliver effective doses while minimizing exposure to surrounding healthy structures. Clinical outcomes, however, have varied. Some studies have reported high rates of local tumor control (up to 97%), whereas others have shown more moderate control levels (ranging from 40% to 71%) and overall two-year survival rates between 18% and 57%.

Among the major risks of radiation therapy is injury to the healthy lung, particularly the one on the side opposite to the irradiated area. Fortunately, increased clinical experience and improved dosing strategies have led to a reduction in these complications. Importantly, radiation therapy is not recommended prior to lung-sparing surgeries like P/D or extended P/D due to a heightened risk of toxicity. However, adjuvant radiation following such surgeries can be considered under controlled trial conditions at centers with relevant expertise.

Advancements in radiotherapy, particularly IMRT, have made it possible to better spare non-cancerous tissues while still delivering effective treatment. Nonetheless, adverse effects such

as severe pneumonitis (grade 3 or higher) remain a concern, occurring in around 20% of patients according to some reports. The risk of such complications increases with larger radiation fields and higher doses.

In centers with the capability and experience, adjuvant or neoadjuvant hemithoracic radiation therapy may be offered using approaches like IMRT, 3D CRT, or even proton therapy, depending on patient eligibility. One previously considered approach—prophylactic radiotherapy to prevent implantation metastases after pleural interventions—is no longer routinely recommended. Clinical trials have failed to show a meaningful benefit in either survival or quality of life from this preventive strategy. Some early studies had suggested a lower rate of subcutaneous nodules in patients receiving prophylactic radiation, but more recent and robust data have not confirmed these results.

For patients who do develop implantation metastases—confirmed through histological examination—adjuvant radiation can be considered as a treatment option. Electrons may be particularly effective in treating superficial lesions like these. In cases of localized but asymptomatic recurrence, treatment decisions should be individualized and made by a multidisciplinary team. The team should weigh all therapeutic options to select the most appropriate course of action.

Radiation therapy also has a well-established role in palliative care. It can provide symptom relief and local disease control, particularly when delivered via advanced techniques such as IMRT. Standard palliative regimens—such as 3 Gy over 10 sessions, 4 Gy over 5 sessions, or a single dose of 8 Gy—are commonly used depending on the clinical situation. Since life expectancy is limited in many palliative patients, long-term side effects, such as those associated with stereotactic body radiation therapy, are generally less concerning.

Data from symptom-focused studies, including the SYSTEMS-1 trial, indicate that palliative radiotherapy—such as 20 Gy given in five fractions—can provide meaningful pain relief in nearly half of treated patients [4,18,35].

Immunotherapy

The effectiveness of immunotherapy in treating peritoneal mesothelioma is still uncertain and under discussion. Further research, including well-designed randomized controlled trials, is necessary to improve the accuracy of clinical staging, better define surgical eligibility, and fully understand the potential advantages and side effects of immunotherapy in this context.

Checkpoint inhibitors, especially nivolumab, have shown promise in second-line treatment of peritoneal mesothelioma (PM) after failure of platinum–pemetrexed chemotherapy. Several single-arm studies reported disease control and survival benefits, particularly in patients with epithelioid histology, while PD-L1 expression did not consistently predict outcomes.

The phase 3 CONFIRM trial confirmed that nivolumab improves progression-free and overall survival compared to placebo in heavily pretreated patients. Pembrolizumab has also shown some activity in early trials, but the phase 3 PROMISE-MESO trial did not demonstrate a significant survival advantage over chemotherapy.

Other agents like avelumab have shown modest efficacy, with better responses in PD-L1-positive patients. Combination immunotherapy, such as PD-1 and CTLA-4 blockade, has shown more encouraging results. Trials like NIBIT-MESO-1, INITIATE, and MAPS2 demonstrated higher response rates and improved survival, though at the cost of increased toxicity.

First-line immunotherapy with ipilimumab and nivolumab has become a new standard of care based on the CheckMate 743 trial, especially for patients with non-epithelioid histology, where the survival benefit was most pronounced. This led to approval in many countries, though in some, such as Italy, its use is restricted to non-epithelioid cases. Emerging biomarkers, like inflammatory gene expression signatures, may help predict response.

Finally, the IND.227 study showed that adding pembrolizumab to first-line platinum-based chemotherapy slightly improved survival and response rates, with the greatest benefit again seen in non-epithelioid subtypes [2].

Vaccine

The goal of vaccines is to activate the immune response to attack mesothelioma cells [36]. Dendritic cell (DC) vaccines aim to stimulate T cells multiplication and activate both CD4+ and CD8+ T cells by showing them tumor-specific antigens, which helps CD8+ T cells to invade the tumor site [18,37,38]. In their randomized phase 2/3 trial, Aerts Joachim G et al. assessed the efficacy of MesoPher, a dendritic cell vaccine, in pleural mesothelioma patients following chemotherapy. While the treatment induced immune responses and was generally safe, it failed to improve overall survival [39]. Studies have also examined vaccines containing bacterial components, such as Listeria monocytogenes and Pseudomonas exotoxin A, revealed that they could have therapeutic potential when combined with chemotherapy in the future

[36,40]. A peptide-based vaccine aimed at telomerase, is another vaccine that has been investigated. Research by Haakensen et al. tested if adding a vaccine called UV1 to the cancer drugs ipilimumab and nivolumab helps patients with pleural mesothelioma after after first-line chemotherapy. 118 patients were randomly assigned to receive either ipilimumab and nivolumab alone or combined with UV1. The primary endpoint, progression-free survival (PFS) as assessed by blinded independent review, showed no significant difference between arms. However, patients who got the vaccine showed better response rates to treatment [41]. Attention should also be given to mRNA vaccines, which could have practical uses after further investigation [36,42].

Gene therapy

Another method that could potentially be employed in treatment is gene therapy. Malignant pleural mesothelioma is characterized by a low frequency of activating mutations and a predominance of genomic deletions and other alterations being more prevalent. BAP1 (BRCA1-associated protein-1), CDKN2A/B, and NF2 (neurofibromatosis type 2 gene) are the genes most frequently affected by mutations [21,36]. The most common chromosomal change in pleural mesothelioma, seen in 61 to 88% of cases, is the loss of part of chromosome 9p21, mainly affecting the CDKN2A gene, which helps make proteins that stop tumors from growing (p16INK4A and p14ARF) [36,43]. Abemaciclib, an oral inhibitor of CDK4/6 (cyclin-dependent kinases 4 and 6), may have potential efficacy related to this pathway and was evaluated in patients with p16INK4A-deficient mesothelioma in a phase II clinical trial [44]. BAP1 helps repair damaged DNA through its role in the BRCA1/BARD1 complex. It also regulates gene expression and cell cycle progression by removing ubiquitin from histones [43]. In the The Mesothelioma Stratified Therapy (MiST) phase II trial, rucaparib, a PARP inhibitor, showed promising results in patients with advanced mesothelioma, especially in cases with cytoplasmic BAP1 loss or BRCA1 deficiency. More than half of the patients experienced disease control at 12 weeks, and nearly a quarter maintained it at 24 weeks [45]. Furthermore, the NF2 gene, which encodes tumor-suppressing Merlin protein, exhibits the highest rate of gene inactivating mutations within the Hippo signaling pathway in mesothelioma [36,46].

Palliative treatment

In pleural mesothelioma, palliative treatment primarily focuses on enhancing patients daily functioning and comfort by alleviating symptoms. As reported in the research conducted by Wakefield et al., from January 2016 to December 2021, a total of 181 cases of pleural mesothelioma were documented. Dyspnea (34% of patients) and pain in the chest (19% of patients) represented the predominant symptoms at diagnosis [47]. One of the palliative treatment options is surgery, which can be used to manage pleural effusion, a frequent symptom of pleural mesothelioma. A typical method in this case is talc pleurodesis. Surgical interventions aimed at symptom control should be performed using minimally invasive approaches. Radiotherapy is another palliative strategy, particularly for patients experiencing pain due to chest wall infiltration or involvement of other thoracic regions. However, there's no clear evidence from clinical studies about the efficacy of radiotherapy in relieving symptoms such as dyspnea or cough [21,15].

Prognosis and therapeutic challenges

Mesothelioma, unfortunately, has a poor prognosis. The median survival time for this tumor is approximately 12-18 months [1,48]. More than 90% of patients die within five years of diagnosis [4]. The study showed that patients with poorer performance status, higher ECOG scores, and non-epithelial histology had a poorer prognosis and ultimately a higher risk of death [48]. Due to difficult diagnostics, the cancer is usually diagnosed in a late, advanced stage. The standard treatment is still chemotherapy and immunotherapy. Surgical procedures can only be used in a few, selected patients, due to the high risk of complications [1,4,15]. Another challenge is finding biomarkers that would facilitate the selection of a specific treatment for the patient, such as targeted therapy or immunotherapy. Further research into combining immunotherapy with chemotherapy is also important [4,15,22,34,49]. The use of nivolumab and ipilimumab as immunotherapy shows promising results for some patients [43]. The CheckMate 743 study showed that the combination of nivolumab and ipilimumab improves overall survival compared to standard chemotherapy. Unfortunately, patients ultimately did not derive long-term benefit from immunotherapy [37,49]. Once the disease progresses, the choice of treatment regimen is limited in the second line of defense. In phase II studies, vinorelbine and gemcitabine with ramucirumab show therapeutic benefits, but they are not approved for

second-line treatment after previous immunotherapy [49]. Despite numerous studies and continuous progress in treatment, pleural mesothelioma remains a challenge. Delayed diagnostics and late diagnosis lead to limited effectiveness of treatment methods and high mortality [1,4,15,22,34,49]. Additionally, a small number of tissue samples and rare occurrence of the disease make clinical trials difficult [43]. A detailed, efficient diagnostic stage and participation in more clinical trials are necessary to improve patient prognosis [1,4,15,22,34,37,49].

Future research directions

Pleural mesothelioma is a rare cancer. Despite the recent increase in randomized controlled clinical trials, there are still too few of them. Research is ongoing on new substances used in immunotherapy. Currently, the most important in the research phase are bispecific antibodies, cell therapies using chimeric antigen receptors, which are directed at MPM antigens. The future is also becoming therapy directed at tumor suppressor genes [49]. In pleural mesothelioma, tumor cell suppressor genes are inactivated, for which targeted therapy is difficult to develop [50]. Recent studies have questioned the importance of surgical cytoreduction in the treatment of this disease and left many questions unanswered [5]. Currently, research is being conducted on therapeutic targets and combinations of combined treatment. Oncolytic viruses are playing an increasingly important role, and biomarkers that enable targeted therapy are being sought [36,37,50]. Future research directions also focus on the development of CAR-T therapy against mesothelin. This antigen is abundant in MPM, but is rarely found in healthy cells [37,49]. Additionally, sequencing of cellular RNA and cell nucleus may influence the emergence of new molecular targets [50]. The treatment is directed at combining several therapies based on an individual molecular profile, so that the treatment is tailored to the appropriate histological subtype of the tumor [36,37].

Conclusion

Pleural mesothelioma poses a therapeutic challenge due to its aggressive course, resistance to treatment, and frequent diagnosis at an advanced stage. Despite progress in understanding the pathogenesis of the disease, including the role of asbestos exposure and genetic mutations (BAP1, CDKN2A), the prognosis remains poor, with median survival estimated at 12-18

months. Current treatment strategies include chemotherapy based on a combination of cisplatin and pemetrexed, immunotherapy (nivolumab with ipilimumab in non-epithelial subtypes), and, in selected cases, surgery. Unfortunately, the benefits of these methods are often limited by adverse events, disease relapses, and resistance to therapy. A significant problem also remains the lack of reliable biomarkers for early detection of the disease and monitoring of response to treatment.

Promising research directions include the development of targeted molecular therapies (e.g. PARP inhibitors in BAP1 mutations), new forms of immunotherapy (CAR-T therapies, bispecific antibodies) and the search for sensitive biomarkers. Optimization of multidisciplinary strategies combining local and systemic treatment methods is also crucial. Due to the rarity of the disease, international cooperation is necessary to conduct clinical trials on an appropriately large scale. Despite some progress, pleural mesothelioma remains a disease with a poor prognosis, which requires further intensive research to improve diagnostic and therapeutic methods.

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