

Mesothelioma - Diagnosis and treatment

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ABSTRACT

Malignant pleural mesothelioma (MPM) is a highly aggressive type of cancer more prevalent in males, although its most common etiology is exposure to asbestos fibers. Improvements in the prognosis of the disease are prevented due to the late manifestation of the disease, difficulties in diagnosis, and inadequate conventional treatments. In recent years, anti-cancer immunotherapy and treatments consisting of single or combined checkpoint inhibitors have been tested. Although programmed death-1 receptor, programmed death-ligand 1, and cytotoxic T-lymphocyte-associated protein 4 immunosuppressant checkpoint agents are promising for future developments, the studies showed that these approaches are currently inadequate due to toxicity problems and poor results. Despite the better understanding of carcinogenesis with new therapeutic approaches, further therapeutic research is needed for the treatment of MPM. A better understanding of multidisciplinary approaches is required to improve the prognosis of the disease and patient survival. Thus, it will be possible to develop more effective treatment strategies.

Keywords: Asbestos, cancer, checkpoint agents, CTLA4 protein, mesothelioma, PD-1 inhibitor, PD-L1 inhibitor.

Mesothelioma is a rare and highly aggressive type of cancer that originates from the mesothelial cells of the pleura or serosal surfaces such as the peritoneum, pericardium and tunica vaginalis. It is most commonly seen in the pleura (65-70%), followed by the peritoneum (30%), pericardium, and tunica vaginalis (1-2%).^[1] This type of tumor, associated with somatic and germline mutations, tends to envelop organs and body cavities and compress them. Mesothelioma originating from the pleura is called malignant pleural mesothelioma (MPM). The relationship with asbestos, which is the most common cause of the disease, was first revealed by Wagner^[2] in 1960. The asbestos mineral is known for its fibrous structure and its frequent presence in nature. The inhalation of asbestos fibers to the lungs may lead to fibrinogenic and mutagenic events in the lung tissue. It has become an occupational disease in developed countries due to its frequent use in the industry.^[3] Asbestos

is present in various regions of the world, and there is a very high incidence of mesothelioma in Turkey's Cappadocia region.^[4] In the 1960s, the number of cases was recorded in some countries to be defined as the pandemic of the period. Although asbestos production was tried to be controlled with some legal regulations in the 1970s, the incidence of the disease continues to increase today.^[5] However, it is known that the latent period is between 20 and 40 years.

EPIDEMIOLOGY

Malignant pleural mesothelioma, which can be considered an industrial disease, is most commonly seen in industrialized countries.^[3] The incidence of mesothelioma in countries such as Australia and England is higher than in other countries.^[3] The high incidence of mesothelioma in Turkey, particularly in the Cappadocia region (Karain, Eski Sarıhıdır ve Tuzköy), is known

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worldwide. The endemic exposure of erionite and asbestos is the main reason for the high incidence in Turkey.^[3] The mesothelioma-asbestos relationship can be compared to the lung cancer-smoking relationship. Fifty percent of death cases in this region are caused by mesothelioma.^[6] It is known that inhalation of fibrous minerals such as asbestos triggers pro-inflammatory activities in the body and predisposes to mesothelioma. Since mesothelioma is an extremely rare tumor, the unusual mortality rate has led to important studies on the genetic predisposition of the disease.^[4] In addition, the fact that the incidence continues to increase even today shows that asbestos-type minerals, whose use was restricted by legal restrictions in the 2000s, are still used.^[6] According to the data of the World Health Organization (WHO), the recorded survival duration after the diagnosis of mesothelioma varies between 9 and 12 months.^[7] It is more common in males than females.^[7] Although the mesothelioma-asbestos relationship has been proven by many studies, several studies on malignant pericardial mesothelioma (incidence rate of 1 to 2% compared to other mesothelioma types) have not found an association with asbestos.^[6-8] Several factors that trigger non-asbestos mesothelioma: non-asbestos fibrous minerals (erionite, balangerite, fluoro-edenite), radiation, simian virus 40 (SV40), tumor suppressor BAP1 gene, chronic serosal inflammation, spontaneous mesothelium.^[9]

MESOTHELIOMA DIAGNOSIS

Malignant pleural mesothelioma is a rare type of cancer that is difficult to diagnose, and it has no specific clinical symptoms. Although symptoms such as difficulty in breathing, pain, loss of appetite and weight loss are generally observed in patients, the disease is reported late because these symptoms are often ignored. In addition, the duration between the patient's admittance to the hospital with symptoms and the diagnosis of mesothelioma is more than 100 days.^[10] All of this leads to the fact that the tumor can be diagnosed almost in its final stages. Early diagnosis is very difficult due to its silent progression and the long latent period.^[11] Mesothelioma develops in the pleural space at a rate of 85%, while the remainder is generally in the peritoneum.^[11] During the diagnosis, aggressive and destructive mesothelioma should be distinguished from

benign proliferation and metastatic carcinomas. However, this is quite difficult since benign mesothelial proliferations and MPM morphologies that can metastasize even to distant tissues overlap with each other.^[12] Consequently, diagnostic sensitivity differs between 30 and 75% with cytological examination alone.^[13] This range shows that cytological examination alone is not sufficient for diagnosis. Morphological and immunohistochemical biomarker examinations should be performed together for accurate histological diagnosis. Adjunct diagnostic techniques such as immunohistochemical stains are indispensable for a complete diagnosis. Pathological, radiological, and clinical findings should be evaluated together in the diagnosis of MPM.

ESTABLISHING THE DEFINITION OF MESOTHELIAL ORIGIN

Establishing mesothelial origin by immunohistochemistry is the first and most important step in the diagnosis. According to recent publications guiding this issue, mesothelioma and epithelial cell biomarkers can provide 80% reliability in the diagnosis and origin identification of mesothelioma.^[12] Since a single immunohistochemical marker does not show high sensitivity or specificity, they recommend using a panel of at least two immunoreactive and two non-immunoreactive markers to establish the diagnosis of mesothelioma. In addition, it is important to use a proven immunomarker panel.^[14] Claudin-4, which has recently been identified as an excellent biomarker in the differentiation of mesotheliomal tissue, is a good example. Claudin-4, which is found in epithelial tissue proliferation, provides 95 to 100% reliability as a biomarker.^[15] Programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) biomarkers, which are the most known for mesothelioma and open new horizons in treatments, will be explained in more detail in the immunotherapy section.^[16]

TECHNIQUES USED IN THE DIAGNOSIS OF MESOTHELIOMA

The first technique used in diagnosis is an imaging technique. Chest radiography

(CXR), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) are some of the options for imaging techniques. Chest radiography is used to identify localized tumor masses and pleural effusions that are late for diagnosis. The tumor crust covering the pleura in the lung is quite prominent at this stage. Pleural plaques can be visualized in CT. Interlobular septal thickening and some pleural-based lesions can be detected with this technique.^[17] Magnetic resonance imaging is generally used to evaluate tumor invasion, and it contributes to the staging of the involvement of the brachiocephalic vessels, chest wall, mediastinal structures, or diaphragm, particularly in patients considered for surgery. In addition, it is beneficial in the planning of radiation therapy (RT).^[18] Positron emission tomography shows how much the chest wall is invaded by this malignant tumor. It is also widely used to locate the tumor if it has metastasized. Thus, it enables the staging of the tumor.^[19] Although all patients with a diagnosis of MPM will receive chemotherapy, staging will show how much the patient will benefit from surgery or if they are suitable for surgery. Histopathology is the basic diagnostic technique in mesothelioma. Immunohistochemical evaluation, which is a part of histopathological evaluation, also plays a more important role in the diagnosis of mesothelioma in recent years. Closed biopsy, video-assisted thoracoscopic biopsy or direct thoracoscopic biopsy methods, which offer a higher probability of definitive diagnosis, are also used.^[19] Biomarkers such as calretinin, cytokeratin 5/6, PD-1, BAP1 tumor suppressor gene, PD-L1, and CTLA4 are sought to support the diagnosis of mesothelioma in tissue.^[12] These markers have an important role in distinguishing MPM from other cancer types.

Fluid and cell samples should be taken from the tumor mass for cytological diagnosis and stained with appropriate methods. Blood cells are usually found in cancerous pleural fluids.^[20] Although this technique is not always sufficient for a complete diagnosis, it is known to be crucial.

The presence of serum proteins associated with mesothelioma is also investigated by a blood test. However, the sensitivity of this technique is low. Soluble mesothelin-related peptides (SMRP) are peptide fragments of mesothelin,

a glycoprotein found in mesothelial cells and overexpressed in mesothelioma cells. Soluble mesothelin-related peptides are not elevated in sarcomatoid mesothelioma and have limited sensitivity in other histological subtypes. These may also be elevated in other malignancies, so they have limited diagnostic utility. In a meta-analysis, it was reported that the sensitivity of SMRPs ranged between 19 and 68%.^[21] In addition, markers such as fibulin-3 and osteopontin in the serum or pleural fluid are being investigated. In addition to the markers, deterioration in pulmonary function tests is also a sign of the disease. However, its use is very limited due to the presence of many diseases that can affect pulmonary function tests. The changes observed in the patients regarding these tests during the follow-up provide information about the progression of the disease. These tests measure how much breathing is restricted by the change in expiratory flow rates.^[10]

HISTOPATHOLOGICAL SUBTYPES OF MALIGNANT MESOTHELIOMA

Malignant pleural mesothelioma is classified into three histological subtypes. These subtypes are epithelioid, sarcomatoid, and biphasic (mixed-phase).^[22] This classification is used in the differential diagnosis of both benign and malignant lesions, although there are several unusual and rare variants. However, the immunohistochemical examination is guided by this subclassification. The epithelioid variant is the most common and accounts for approximately 60% of all mesotheliomas.^[22] Typical histological appearances of this subtype include tubulopapillary, acinar (glandular), adenomatoid and solid epithelioid patterns. Sarcomatoid mesotheliomas consist of malignant spindle cells that can mimic MPM tumors such as leiomyosarcoma or synovial sarcoma. Desmoplastic mesothelioma, which consists of light tumor cells between dense bands of collagen stroma, is considered a subtype of sarcomatoid mesothelioma. Biphasic or mixed mesotheliomas have epithelioid and sarcomatoid features. However, multiple tissue sections or larger samples may be needed to demonstrate both components. Besides synovial sarcoma, other biphasic tumors are typically considered in this differential diagnosis.^[22]

STAGING OF MALIGNANT PLEURAL MESOTHELIOMA

Chest and upper abdominal CT scanning with intravenous contrast are typically performed for initial radiographic staging. However, PET-CT can more accurately identify metastatic foci and determine the indication for surgical resection. Histopathological diagnosis should be made in patients who are evaluated as inoperable after PET-CT findings. When intrathoracic lymph nodes, contralateral pleural or abdominal metastases are suspected, metastasis can be confirmed by performing laparoscopy with endobronchial ultrasound (EBUS)/endoscopic ultrasound or mediastinoscopy, contralateral thoracoscopy, and histological biopsies, respectively. In addition, MRI may be useful in certain situations to delineate the presence of local tumor invasion into adjacent structures such as the mediastinum, chest wall and diaphragm.^[23]

Malignant pleural mesothelioma is the only type of mesothelioma that can be staged. TNM staging, which includes the tumor size (T), the lymphatic spread (N), and the distant metastasis (M) stage, is used in the staging of MPM. It is staged from I to IV according to TNM scores. Stages can be summarized as follows: Stage I, the condition in which the disease is limited to the ipsilateral pleura; Stage II, additional ipsilateral lymphatic involvement; Stage III, the tumor involving deeper tissue or contralateral lymphatics; Stage IV, distant metastasis.^[32] In addition, it is seen that there are different guides in the literature that help stage mesothelioma. Staging can be done with the mitotic rate, nuclear score, and presence/absence of necrosis of the tumor. Mitotic rate in nuclear grading is calculated as follows: 1=low level (1/2 mm²), 2=intermediate (2-4/2 mm²), 3=high level (5+/2 mm²). The nuclear score is defined as follows: 1=mild, 2=moderate, 3=severe. When these two features are calculated, nuclear grading is done and a conclusion is reached by considering the presence of necrosis in the two-phase staging. Nuclear grades according to total scores are as follows: 2 or 3=nuclear Grade I, 4 or 5=nuclear Grade II, 6=nuclear Grade III.^[21,22] In two-phase staging, the low grade is defined as nuclear Grade I and II/no

necrosis; the high grade is defined as nuclear Grade II/with necrosis nuclear Grade III/with or without necrosis.^[24,25]

MOLECULAR TEST FOR MALIGNANT PLEURAL MESOTHELIOMA

Genetic analysis of MPM tumors is characterized by frequent oncogenic changes in tumor suppressor genes such as BAP1. In rare circumstances, genomic sequencing of the tumor is used to identify familial cases of mesothelioma.^[26] However, tumor genomic sequencing is currently not recommended for routine clinical practice. Heterozygous germline BAP1 mutation is known to cause an autosomal dominant condition called BAP1 cancer syndrome, which causes a genetic predisposition to various types of cancer such as mesothelioma.^[27] Therefore, the identification of oncogenic changes may enable the search for new treatment modalities in the future. Immunohistochemical studies are performed on pleural fluid cytology to detect deletions in the tumor suppressor protein p16 and the gene that encodes it, CDKN2A. These studies aim to detect the loss of BAP1 by fluorescent in situ hybridization (FISH). These tests help distinguish mesothelioma from reactive mesothelial cells. Malignant pleural mesothelioma tumors have potential therapeutic targets. Programmed death-ligand 1 expression is positive in approximately 10 to 40% of MPM cases. In particular, there is a higher frequency of positivity in sarcomatoid mesothelioma.^[28] In addition, PD-L1 expression in the tumor is associated with poorer survival times. The efficacy of immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway in MPM is a current research topic. Cancer-associated antigens, selectively expressed on MPM, are attractive potential therapeutic targets. For example, mesothelin, the cell surface glycoprotein, is selectively expressed on mesothelial cells. Mesothelin is overexpressed in many cancers, comprising approximately 94 to 95% of epithelioid MPM.^[29] Treatments targeting cancer-associated antigens and specific oncogenic changes are currently under investigation.

MALIGNANT PLEURAL MESOTHELIOMA TREATMENT STRATEGIES

Response rates to traditional anti-cancer therapy methods in MPM are poor and inadequate. Many other experimental treatment modalities continue to be explored today, including targeted therapies and immunotherapies. There are several possible treatment modalities for MPM, and the choice of treatment strategy is based on patient-and disease-related factors. The most common treatment options are surgical resection, chemotherapy, RT, and immunotherapy.^[30] Often, a multimodal approach is preferred to increase treatment efficacy and achieve an optimal survival rate. Multimodality therapy can be applied for both curative and supportive purposes.

CHEMOTHERAPY AND TARGETED THERAPIES

The survival time provided by standard platinum-based chemotherapies is between 9 and 12 months, making it necessary to investigate new treatment methods such as systemic chemotherapy. For patients whose tumors cannot be surgically removed and performance is not very poor, the current standard first-line systemic treatment is combination chemotherapy with pemetrexed and platinum-based chemotherapy. Pemetrexed, one of the chemotherapy drugs, is an antifolate agent and inhibitor of thymidylate synthase required for deoxyribonucleic acid (DNA) synthesis. Cisplatin, also one of the chemotherapy drugs, is a platinum-based agent that causes DNA cross-linking. In 2003, Vogelzang et al.^[31] conducted a pivotal phase 3 study of systemic chemotherapy. More than 400 patients with MPM, who did not receive chemotherapy and did not undergo surgery, were treated with either pemetrexed/cisplatin or cisplatin alone. Median survival was 9.3 months in the combination therapy group and 12.1 months in the monotherapy group. A response rate of 16.7% versus 41.3% was observed between the pemetrexed/cisplatin group and the control. In addition, a significantly longer median time to progression was detected in the pemetrexed/cisplatin group (5.7 months) compared to the control group (3.9 months). Folic acid and vitamin B12 supplementation was also found to significantly reduce toxicity

without adversely affecting survival.^[23] In addition, higher toxicity is observed in patients receiving combination chemotherapy.

Pemetrexed and platinum-based induction chemotherapy is the standard treatment for patients with clinical Stage I to IIIA epithelioid or biphasic MPM. Pleurectomy/decortication (P/D) or extrapleural pneumonectomy (EPP) is recommended in patients with a resectable tumor according to chemotherapy response. Adjuvant chemotherapy followed by hemithoracic pleural RT is recommended for patients undergoing P/D. In patients who underwent EPP, sequential chemotherapy and hemithoracic RT are recommended. Chemotherapy is continued in patients who are considered inoperable in the evaluation after neoadjuvant chemotherapy.^[32]

Chemotherapy options are limited in patients who do not respond to treatment. Until 2016, no randomized studies have shown improved survival with an alternative regimen.^[33] Vascular endothelial growth factor (VEGF) is known to play a role in MPM pathogenesis. In a phase III randomized study, the addition of bevacizumab, an anti-VEGF monoclonal antibody, to other chemotherapy drugs, cisplatin and pemetrexed, was found to prolong median survival up to 18.8 months versus 16.1 months.^[34] Therefore, the addition of bevacizumab to therapies may be considered if there are no contraindications. Unfortunately, there are no approved second-line treatments for MPM. Some second-line options include vinorelbine and gemcitabine or nivolumab and ipilimumab for immunotherapy. Vinorelbine and gemcitabine have not been shown to improve survival.^[34]

SURGICAL

The role of surgery in MPM includes the removal of some/all of the peritoneal membrane surrounding the abdomen to achieve a reduction in tumor load.^[35] However, MPM almost always recurs after surgery alone. Although controversial, surgery is recommended as part of a multimodal treatment strategy unless it is inoperable. However, it is known that the presence of nodal metastases, extensive involvement of the chest wall, diaphragm and mediastinum, and non-epithelial histology adversely affect the results of aggressive surgical interventions in this disease. Involvement of the

contralateral hemithorax and distant extrathoracic regions, including intraperitoneal spread, should be considered as contraindications for maximal surgical cytoreduction. In such extensive MPM cases, the probability of complete macroscopic resection is low.^[36] Surgery is not recommended for sarcomatoid MPM as well as patients with advanced epithelioid MPM. Observation is recommended in asymptomatic patients, and systemic chemotherapy is recommended in symptomatic patients.^[32]

There are two options for surgery. The first option is P/D, defined as mediastinal lymph node sampling with gross tumor with or without *en-bloc* resection of the pericardium or diaphragm with complete removal of the pleura and reconstruction. Another method defined as *en-bloc* resection of the pleura, lung, ipsilateral diaphragm, and pericardium is EPP.^[32] The ideal surgical intervention to achieve maximum cytoreduction is controversial. There is no significant difference in survival outcomes between EPP and extended pleurectomy/decortication (EPD) in more than 1000 MPM patients in the National Cancer Database (NCDB).^[36] Pleurectomy/decortication is more preferred by specialists, partly because of the preservation of the lung parenchyma and the theoretical postoperative functional recovery, and its capacity to tolerate further pulmonary injuries.^[36] In 90 MPM patients treated with multimodality therapy, including EPD and photodynamic therapy, between 2005 and 2013, the median survival time was approximately seven years in the early stages and three years in the final stages.^[37]

RADIOTHERAPY

In general, MPM is known to be resistant to RT. However, as a result of current evidence and technological developments in RT, it has been seen that RT can create positive results. With the development of intensity-modulated radiation therapy (IMRT) techniques in the last 10 years, normal tissue protection has increased, and higher dose radiotherapy has been applied to the hemithorax.^[38] In a study conducted with old RT techniques in 1991, toxicity was examined after hemithoracic application of different doses such as 20 Gy, 55 Gy, and

70 Gy (the amount of energy absorbed in a substance exposed to unit radiation/Gray), and it was observed that the side effects were quite high.^[38] However, with the development of RT techniques and the use of IMRT over time, RT has become a part of the standard treatment in mesothelioma.^[39]

The use of RT in mesothelioma can be divided into three main categories: preoperative, postoperative and palliation RT.

Preoperative RT aims to reduce the risk of local recurrence. The rationale for this technique is to prevent recurrence after a needle biopsy of the pleura in many patients. However, it is no longer recommended because preoperative RT could not be shown to have a survival benefit in a multicenter phase III sequential multiple assignment randomized trial (SMART).^[40] In addition, a meta-analysis evaluating five prospective randomized controlled trials on preoperative RT once again showed that prophylactic RT did not provide a statistically significant reduction in the risk of recurrence at the surgical site.^[41]

The application of hemithoracic RT after EPP has changed significantly in the last 15 to 20 years with the development of IMRT techniques. Initial results of studies using IMRT in the treatment of mesothelioma were promising in terms of disease control and toxicity. In a study with 13 patients administered 54 Gy RT at a fraction dose of 1.8 Gy, fatal pneumonitis was observed in six of the patients.^[42] With this study, the importance of the low-dose area in the lung was determined, and the dose restrictions in the normal lung tissue were revised. As a result, there was a significant reduction in lung toxicity. Another study showed that RT after EPP can reduce the likelihood of cancer recurrence.^[43] In routine treatment, hemithoracic RT with the IMRT technique has become the standard treatment for patients undergoing EPP.^[32,44]

A study with 27 patients, enrolled in a phase II study to determine the safety of hemithoracic intensity modulated pleural radiation therapy (IMPRINT) after chemotherapy and P/D, showed that a dose of 50.4 Gy in 28 fractions can be safely administered with or without a Grade IV side effect.^[45] Although the standard recommended dose after P/D is 50.4 Gy in

28 fractions, the dose can be increased up to 60 Gy for residual disease, provided that normal tissue restrictions are not exceeded. Treatment should begin within four to eight weeks of P/D or completion of the last dose of chemotherapy.^[46]

Palliative RT is applied at doses of 20 to 40 Gy in 5 to 10 fractions or a dose of 3 to 4 Gy in advanced stages and patients with poor performance status.^[20,32] However, a supportive treatment plan is required in addition to RT for pain control.

In addition, studies have been conducted on the effects of RT combined with immunotherapy in tumor control.^[47] With these studies, the interactions between radiation and the immune system were investigated. Promising clinical research into this approach has been strengthened by many ongoing studies describing immunotherapy and combining it with palliative radiation. In these studies, the combination of immune checkpoint inhibitors with standard treatments such as chemotherapy, RT, and surgery appears to be a highly promising mechanism for disrupting the tumor microenvironment and facilitating specific activation of the immune system against mesothelioma.^[48] Over the past 15 years, short courses of RT have been found to have an activating effect on the immune system.^[40] Therefore, animal studies have been conducted combining RT with the immune checkpoint blockers of CTLA4, PD-1, and PD-L1 for the treatment of MPM.^[49] Supported by many studies, CTLA4 blockade is a promising immunotherapeutic mesothelioma treatment, and its effect can be enhanced when combined with conventional treatments such as systemic chemotherapy and RT.

IMMUNOTHERAPY

The innovative principle of immunotherapy is that it reprograms the immune system to recognize cancerous cells rather than targeting cancer cells. From a theoretical point of view, immunotherapy can provide long-term disease control and increase survival by limiting tumor spread. In the past 15 years, inhibitor studies for anti-cancer immunotherapy, particularly for immune checkpoint blockers of PD-1/PD-L1 and CTLA4, have been increasing rapidly. It has been observed that inherently to cancer,

immune checkpoints are constantly activated, which creates a negative effect on the immune system.^[50] It has been shown that this leads to a loss of balance between the co-stimulatory and co-inhibitory pathways and thus to an increase in tumor formation. Immune checkpoint inhibitors are now legally approved and used for many cancer therapies.

Considering the inflammatory phenotype of MPM, the use of these agents for the treatment of mesothelioma is very promising. In addition, 20 to 40% PD-L1 expression is found in stromal and mesothelioma cells.^[51] In studies using a single-agent PD-1 or PD-L1 inhibitor for MPM, tumor response is reported in approximately 10 to 20% of patients receiving this therapy.^[52] Cytotoxic T-lymphocyte-associated protein 4 is an immune checkpoint receptor that provides immunological homeostasis by regulating inhibitory signals. Blocking the CTLA4 receptor allows T cell activation and tumor-specific T cells to exert cytotoxic effects on tumor cells. Considering that combining anti-PD-1 or anti-PD-L1 therapy with CTLA4 agent can further increase treatment efficacy, investigating the use of combined checkpoint inhibitors may open new horizons for the treatment of MPM.

The monoclonal antibodies against CTLA4, ipilimumab and tremelimumab, are the main clinically developed therapeutics. Both are human-specific monoclonal antibodies and are known to support T cell activation and increase tumor-specific cytotoxicity.^[53] Ipilimumab is an immunoglobulin (Ig) G1 isotype, while tremelimumab is an IgG2 isotype that causes less toxicity to body cells, and the half-life in the body is twice that of ipilimumab. Given this information, tremelimumab appears to be a potentially better therapeutic than ipilimumab.^[54] However, tremelimumab continues to be investigated at different doses as a monotherapy and in combination treatments with different therapeutics on different tumors, including MPM. In a phase II study investigating the efficacy of tremelimumab in chemotherapy-resistant patients, 29 patients received tremelimumab with no complete response overall, and two (7%) patients had a sustained partial response. However, the disease was controlled in 31% of patients, with a median progression-free survival of six

months.^[55] In a randomized prospective study, 571 patients were divided into double-blind placebo and tremelimumab arms. However, there was no statistically significant difference in overall survival between the tremelimumab and placebo groups.^[56]

Nivolumab and pembrolizumab, which are other immunotherapy drugs, represent the first generation of human-specific anti-PD-1 antibodies. Pembrolizumab was approved by the Food and Drug Administration (FDA) in May 2017 for the treatment of treatment-refractory MPM.^[57] In a phase II study investigating the efficacy of pembrolizumab in treatment-refractory patients, PD-L1 expression was more common in peritoneal mesothelioma, although the response rate was higher in pleural mesothelioma than in peritoneal mesothelioma (20% vs. 13%, respectively).^[58] In the PROMISE-Meso trial, patients were randomized to single-agent chemotherapy (gemcitabine or vinorelbine) versus pembrolizumab, and the pembrolizumab arm had no superiority in either disease-free survival or overall survival.^[59] Combination therapy combining anti-PD-1 and anti-CTLA4 agents such as nivolumab and ipilimumab has been tried in several clinical trials. As a result of these studies, it was determined that it causes between 50 and 80% tumor response in advanced melanoma.^[60] However, although combined immunotherapy has a higher response rate than monotherapy, it appears to cause higher levels of toxicity in the body.^[61] Therefore, the fact that combined immunotherapy may yield better clinical outcomes than monotherapy is still an assumption. Another study in mice with mesothelioma shows that anti-CTLA4 antibody therapy reduces tumor growth and improves survival.^[49]

In conclusion, the use of immunotherapy for MPM, whether as a monotherapy or in combination, is still in its very early stages. However, the effect of combined/mono checkpoint inhibitors combined with chemotherapy on survival is worth investigating if treatment toxicity can be kept at acceptable levels. Immunotherapy has the potential to be the beginning of a new era for mesothelioma due to reasons such as the inadequacy of traditional therapies in the treatment and the overall survival time of less than one year after diagnosis. Checkpoint

inhibition and addressing the microenvironment are more fascinating options than conventional mesothelioma treatments. In addition, with the technological developments in RT, it is possible to apply higher doses to the tumor with better normal tissue protection. Many further studies, including genetic studies, are needed to develop new agents for the treatment of MPM.

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