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Established and new treatment roadmaps for pleural mesothelioma: opinions of the Turkish Collaborative Group

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ABSTRACT

Pleural mesothelioma (PM) is a cancer of the pleural surface, which is aggressive and may be rapidly fatal. PM is a rare cancer worldwide, but is a relatively common disease in Turkey. Asbestos exposure is the main risk factor and the most common underlying cause of the disease. There have been significant improvements in diagnoses and treatments of many malignancies; however, there are still therapeutic challenges in PM. In this review, we aimed to increase the awareness of health care professionals, oncologists, and pulmonologists by underlining the unmet needs of patients with PM and by emphasizing the need for a multidisciplinary treatment and management of PM. After reviewing the general information about PM, we further discuss the treatment options for patients with PM using immunotherapy and offer

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evidence for improvements in the clinical outcomes of these patients because of these newer treatment modalities.

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Introduction

Pleural mesothelioma (PM) is a rare and aggressive cancer of the pleural surface. PM is a relatively chemoresistant disease and has a long median survival time (eg, 9-12 months).[1] Although significant improvement has been made in diagnoses and treatments of many malignancies, therapeutic challenges remain in PM. This review aims to enlighten the unmet needs of patients with PM and to emphasize the need for a multidisciplinary treatment and management of PM by increasing the awareness of health care professionals, in general, and oncologists and pulmonologists, in particular. For this purpose, after reviewing the general information about PM, the options for the treatment of patients with PM are further discussed by referring to similar or different aspects between Turkish population and literature data, when appropriate.

Aetiology and epidemiology

PM is the most encountered form, which accounts for 65%-70% of all cases, followed by peritoneal mesothelioma (30% of all cases) and pericardial mesothelioma (1%-2% of all cases).[1] Mesothelioma is more common in males than females due to occupational exposure to asbestos. The incidence rate of mesothelioma varies among countries; per 100,000 people, it is 0.9 for males and 0.3 for females in USA, and 1.7 for males and 0.4 for females in Europe.[1] According to the data of the Ministry of Health in Turkey, the incidence has been reported to be around 1 in 100,000 people; however, it is epidemic in some regions (the incidence is 1000 times higher in Karain village in Cappadocia than in other regions).[2]

Asbestos exposure, either occupational or environmental, is the most important risk factor for the development of PM.[3,4] The use of asbestos has been banned in many countries, including Turkey, since the 1990s.[1] The relative risk of various occupational exposures has been extensively addressed in the literature.[5,6] Although many factors may increase a person's risk of PM, the exposure to inorganic fibres, asbestos, and erionite remain the only known causal factors of PM in Turkey. Simian virus 40 has been implicated in the aetiology of PM[7]; however, it is not a cofactor in Turkey.[8] The predictive role of the human leukocyte antigens (B41, B58, and DR16) in PM has also been addressed but still needs to be further investigated.[9] Pedigree analysis in affected families in the Cappadocian villages of Turkey also suggests a genetic susceptibility that is inherited in an autosomal dominant pattern, raising the possibility of a specific gene-environment interaction.[10] However, a recent study investigated PM in immigrants from the Cappadocian villages to Sweden. The study was conducted in 2 genetically similar populations, with and without erionite exposure, and concluded that genetic factors might have minor importance in the PM development, although exposure to erionite remains the leading cause.[11]

Pathology, molecular changes, and biomarkers

The international evidence-based comprehensive classification of the World Health Organization (WHO) updated in 2021 is the basis of pathological approach to PM.[12] Traditionally, 3

major subtypes are recognized as epithelioid, biphasic, and sarcomatoid, which have an impact on prognosis and treatment. It is well-known that the most aggressive subtype is sarcomatoid; however, some histological patterns of epithelioid mesothelioma have recently indicated that it also shows an aggressive behaviour.[12] In Turkey, the epithelioid histology of PM is more common (71%) than nonepithelioid histology. Similar to the data observed worldwide, the prognosis of nonepithelioid PM is worse than that of epithelioid PM in Turkey.[13]

The WHO has recommended a grading system for epithelioid mesotheliomas depending on nuclear atypia, mitotic figures, and necrosis for better prognostic stratification of patients.[12] Both histological and cytological examinations are well accepted for the diagnosis of PM. However, sarcomatoid mesotheliomas practically do not shed cells into the pleural fluid and can be rarely recognized cytologically.[14-16]

Ancillary tests are crucial for the correct pathological interpretation of PM and immunohistochemistry is widely used for this purpose. A set of antibodies are needed including both mesothelial and nonmesothelial markers, which are discussed in detail within the guidelines published in the literature.[14,15] Different subtypes have their own differential diagnosis and immune panels are designed accordingly. Immunohistochemically, loss of BRCA1 associated protein-1 (BAP1) nuclear expression and p16 (CDK2NA; 9q21) homozygote deletion detected by fluorescence in situ hybridization or MTAP immunohistochemistry are very useful tests in differentiating mesotheliomas from reactive mesothelial proliferations, which may be a problem especially in cytological samples and small biopsies.[15,17-21]

In contrast to many other malignant tumors, genomic data on PM is still limited. Tumor mutation burden is characteristically low; most frequent alterations are in tumor suppressor genes; and deletion in CDK2NA is a common finding.[19,22,23] BAP1 is another important gene in the pathogenesis of mesothelioma; germline inactivation is present in a subset of patients.[19,22,24,25] Genomic subtype with TP53 and SETDB1 mutations and an extensive loss of heterozygosity have been described in some patients with PM. A strong expression of the immune checkpoint gene VISTA has been shown in epithelioid PM.[25] Deletions of SUFU locus (10q24.32) have been observed, which resulted in disordered expression of transcripts from Hedgehog pathways and the T-cell synapse including VISTA. Codeletion of interferon type I genes and CDKN2A has been detected as the predictor of poor survival. Deletions in RB1, RASSF7 amplification, and NF2 or LATS1/2 mutations have been also shown in patients with PM.[26]

Mutations in DNA repair genes have been demonstrated. The tumor microenvironment (TME) of PM is also under investigation from all aspects.[22,27] Immune-suppressive cells such as M2 macrophages, myeloid-derived suppressor cells, and regulatory T cells are present within TME.[22] In a retrospective multicenter study, histological variables such as necrosis, mitosis, grading, Ki-67 score, tumor infiltrating lymphocytes, and PD-L1 expression have been evaluated and compared with clinical findings. The results have shown that TME rich in cytotoxic T lymphocytes are associated with the presence of more macrophages, higher levels of PD-L1 expression in tumor cells, and histological findings related with aggressive behavior; overall survival has also been reported to be shorter in these cases.[28] In another study, PM cases have been investigated for their immune gene expression profile and PD-L1 expression (both in tumor cells and infiltrating immune cells). The results have revealed that 60% of the patients are suitable candidates for immunotherapy either by their PD-L1 expression or immune gene profiling.[29] The tumor infiltrating immune cells and stromal elements within the tumors hold key prognostic and predictive implications.[22,28] There is a strong rationale for thoroughly mapping TME in mesotheliomas for the success of targeted therapies.[30]

Blood-based biomarkers have been extensively investigated for their diagnostic potential in PM, including soluble mesothelin, osteopontin, and fibulin-3.[23,31] A meta-analysis has shown the sensitivity and specificity of mesothelin (the first candidate to be used in clinical practice) range between 19% and 68% and 88% and 100%, respectively.[23] Four other potential biomarkers for PM are LOX, LOXL1, LOXL2, ZFPM2, which are found to be superior to sulfatase 1, thrombospondin 2, and cadherin; they have given comparable results with fibulin-3 and mesothelin.[32] Lymphocyte-to-monocyte ratio (LMR) and neutrophil-to-lymphocyte ratio (NLR) may also be important biomarkers.[33] Elevated LMR has been reported to be associated with prolonged

survival,[34] in contrast elevated NLR has been found to be related to poor prognosis.[35] Increase in the level of the high mobility group box-1 protein in serum has been demonstrated as a potential diagnostic biomarker.[36] MicroRNAs are another group of markers under investigation for their diagnostic and prognostic abilities in several tumor types including PM.[37] Biomarkers are needed not only for early diagnosis but also to predict prognosis and response to treatments. An ideal biomarker is defined as "inexpensive, reproducible, easy to obtain, and easily sampled with a minimally invasive technique, making blood-based tests prime for investigation."[33]

Clinical aspect

Clinical symptoms reflect extension of disease; shortness of breath and chest pain or painful breathing are the most common symptoms. Chest pain can be caused by effusion or tumor itself.[38] Shortness of breath is often initially due to pleural effusion; encasement caused by growing intrathoracic tumor is the major cause of breathlessness as disease progresses.[39] As a result of circulating cytokines, released by both tumor and host in response, fatigue, cachexia, fever and night sweats, weight loss, cough, chest wall mass, and lymphadenopathy are the other symptoms and signs.[39-41] Superior vena cava obstruction, laryngeal nerve palsy, dysphagia, and pain in the lower back or rib area often occur at preterminal stage and are the results of the tumor invasion.[38,41] Thrombocytosis, hypoalbuminemia, elevated erythrocyte sedimentation rate, and anemia are often detected at advanced stages of the disease.[8,10] Some patients are asymptomatic in the early stages of the disease but show imaging abnormalities for various reasons. Thus, these patients appear to have longer survival, probably because of the early diagnosis.[38,40,42]

Challenges in PM diagnosis

As the clinical symptoms are usually nonspecific, almost all patients should be examined with radiological imaging techniques, which provide valuable diagnostic and staging information. A unilateral pleural effusion and/or thickening can be usually observed by chest radiography and a diffuse or nodular pleural thickening is often observed on a computerized tomography (CT) scan indicating the presence of the PM pathology. An 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/CT can be used to provide useful functional information on pleural lesions, but it has limited contribution in the staging of PM, since distant metastases are rare in this locally aggressive tumor. PET-CT may contribute to the assessment of lymph node metastasis. Therefore, PET-CT evaluation is more important in patients who are scheduled for surgical treatment.[43] The functional magnetic resonance imaging seems to be a promising diagnostic tool but has not been validated yet.[44] These clinical diagnostic methods are in use in Turkey as in the rest of the world.

Video-assisted thoracoscopy, not traditional thoracoscopy, is stated as a gold standard for investigating an undiagnosed pleural effusion.[44] Under thoracic ultrasonography, pleural biopsies can also be performed.[44] However, other biopsy methods such as blind closed-needle biopsies and image-guided pleural biopsy may be more appropriate only in selected cases.[44] The sensitivity of blind closed-needle biopsy for malignancy is low and much lower for the diagnosis of PM.[44-48] Thus, it cannot be recommended as a first-line investigation.[47] The sensitivity of image-guided biopsy has been reported in a number of observational series. The ultrasound- and CT-guided biopsies are superior to blind pleural biopsy.[49,50] The role of video-assisted thoracoscopic biopsy is important in PM diagnosis, since it allows evacuation of symptomatic pleural effusion and pleurodesis and lends for staging diagnosis, through the degree of invasiveness.[51-53] Video-assisted thoracoscopy for pleural malignancy has a high diagnostic value. Its overall diagnostic sensitivity has been reported as 92% after reviewing the results of 22 case series of 1369 patients.[54]

Staging of PM is difficult due to limitations in current imaging techniques, specifically in the accurate assessment of T status and nodal involvement.[55] It is also difficult to evaluate descrip-

tors such as lung invasion or fissure invasion in collapsed lung due to pleural fluid. It may be a problem to evaluate lymph node involvement due to close proximity to the pleural tumor. Video-assisted thoracoscopy, with additional mediastinoscopy to assess suspected nodal disease, is superior to CT and is currently the gold standard for early PM staging.[56] However, not all patients are suitable to undergo this procedure and therefore, image-based staging is often performed for many PM cases.[44]

Staging systems reported in the literature include the Butchart staging system, the Brigham staging system, and the tumor node metastasis (TNM) staging system. The recommended classification for clinical use is the TNM staging system, established by the International Mesothelioma Interest Group and the International Association for the Study of Lung Cancer in 1994 and regularly updated. TNM is the most widely-used staging system for the PM, which is able to provide more information.[57-60] However, the staging of PM remains difficult by any standard.[61]

PM treatment modalities

The treatment of PM has progressed, but so far there is no known effective curative therapy and patients with PM have poor survival rates. Clinical practice guidelines on optimal PM treatment have been published by the American Society of Clinical Oncology,[62] the National Comprehensive Cancer Network,[43] and the European Society for Medical Oncology.[63] Surgery should be performed for suitable patients as a part of multimodality treatment involving chemotherapy with or without radiation therapy.[43]

Approach to resectable PM

Surgical resection is considered a mainstay of the treatment in early stage PM. However, it is almost impossible to achieve a microscopically complete resection with surgery alone because of the anatomy of the pleura and PM property to infiltrate the underlying and neighboring structures; as a result, surgery alone is often associated with high recurrence rate, requiring careful selection of patients. Benefiting from surgery also varies according to the PM histology. Epithelioid type provides more benefits than the others, whereas sarcomatoid type has the worst prognosis.[64]

One of the treatment approaches is a combination of cytoreductive surgery (pleurectomy) and a specific adjuvant therapy. Pleurectomy or decortication (P/D) is a cytoreductive surgery in PM treatment. P/D remains an important and widely applicable effective surgical procedure in controlling both pleural effusion and tumor burden in PM cases.[65,66] However, microscopic residual tumor is often left behind after the procedure, most frequently on the visceral pleura, with the ipsilateral hemithorax being the most common side of disease recurrence. Therefore, all recent P/D studies have included neoadjuvant or adjuvant therapy.

In patients with resectable PM, 4 cycles of neoadjuvant or adjuvant cisplatin+ pemetrexed treatment are suggested as a standard procedure. However, neoadjuvant platinum+pemetrexed+bevacizumab is not generally recommended during surgery due to high risk of bleeding.[62] The role of adjuvant or neoadjuvant immunotherapy is under investigation.[62,63]

Extrapleural pneumonectomy (EPP) is another surgical method used in the treatment of PM. This procedure consists of en bloc resection of the lung, visceral and parietal pleura, pericardium and ipsilateral diaphragm, and reconstruction of the pericardium and diaphragm.[67] However, with the results of the randomized MARS study in 2011,[68] it has lost its popularity and is currently applied to only a few selected PM cases. Similar to the global trend, EPP was a preferred surgical treatment for PM in Turkey in the late 1990s and early 2000s[69,70]; however, the results of the MARS study[68] also led to a reduced popularity of this method in Turkey.

Briefly, surgery is an important treatment modality in patients with PM, but not all patients are eligible for surgery. Debates about the efficacy of surgery either before or after chemother-

apy are ongoing and require further investigations. The selection of patients for surgery remains uncertain and there is no agreement between experts. In appropriately selected patients with an acceptable risk profile, surgical resection (extended P/D, P/D, or EPP) as part of a multimodality concept should still be recommended in high-volume experienced centres.[64] To increase the quality of management of PM cases, there is an urgent need for an agreement on "who and when" to proceed with surgery. This can be achieved by increasing quantity and quality of interdisciplinary preoperative work.

Approach to unresectable PM

PM is a highly aggressive type of cancer and most patients are unresectable at diagnosis. Therefore, treatment has traditionally been limited to chemotherapy. First-line and second- or later-line treatment options and clinical studies related to them are discussed below.

First-line treatment

PM is a relatively chemoresistant disease with an objective response rate (ORR) of <15% to single chemotherapeutic agents. ORR increases when combination chemotherapy is used. Until the randomized phase 3 CheckMate 743 study, which reported improvements in OS with nivolumab+ipilimumab as compared to traditional standard-of-care chemotherapy,[71] the combination of pemetrexed and cisplatin was the standard first-line treatment for unresectable PM.[72] Pemetrexed+cisplatin regimen is also the treatment of choice in adjuvant and neoadjuvant setting. As the data regarding pemetrexed maintenance is preliminary, the usual approach is to stop treatment after 4 to 6 cycles of pemetrexed+cisplatin.[73] However, some centers prefer to treat patients with pemetrexed maintenance until disease progression. In those patients with contraindication or intolerance to cisplatin, pemetrexed+carboplatin regimen is a valid alternative.[74] On the other hand, the addition of bevacizumab to pemetrexed+cisplatin regimen has shown significant improvements in the median progression-free survival (PFS) and OS.[75] Due to conflicting results of other trials evaluating the addition of antiangiogenic agents to chemotherapy,[76,77] bevacizumab has not been approved in the first-line treatment in Turkey as well as in most other countries.

In the multicenter, randomized, single-blind trial reported by Vogelzang et al.,[72] pemetrexed+cisplatin treatment (n = 226) was compared with cisplatin alone treatment (n = 222) in patients with PM, who had never received chemotherapy before. They achieved a significantly longer median survival time in the pemetrexed+cisplatin group than in the cisplatin alone group (12.1 months vs 9.3 months). The median time to progression was also significantly longer in the pemetrexed/cisplatin group than the cisplatin alone group (5.7 months vs 3.9 months). Response rates were 41.3% and 16.7% in the pemetrexed+cisplatin group and the cisplatin alone group, respectively. The treatment was well tolerated, although some patients required vitamin supplementation to reduce toxicity. As a result, pemetrexed+cisplatin treatment was found to be superior to cisplatin alone.[72]

A multicenter, randomized, controlled, open-label, phase 3 study, the MAPS trial, was conducted to compare the pemetrexed+cisplatin regimen (n = 225) with the pemetrexed+cisplatin+bevacizumab regimen (n = 223) as a first-line treatment in chemotherapy-naïve patients with PM.[75] The addition of bevacizumab to the treatment provided a significant prolongation in the median OS (18.8 months vs 16.1 months). Hypertension and thrombotic events were more common adverse events (AEs) in the bevacizumab added group. However, despite the risk of these manageable AEs, the pemetrexed+cisplatin+bevacizumab treatment was considered a viable option.[75]

The DREAM trial, an open-label, single arm, multicenter, phase 2 trial, investigated the activity of durvalumab given during and after first-line chemotherapy with cisplatin and pemetrexed in 54 patients with PM with a follow-up of 28.2 months (interquartile range, 26.5-30.2 months).[78] Among treated patients, 57% (95% CI, 44-70) were alive and progression-free at 6-month follow-up. A total of 60 serious AEs occurred in 29 participants; 5 of which were consid-

ered possibly related to durvalumab. Neutropenia (7 [13%] patients), nausea (6 [11%] patients), and anemia (4 [7%] patients) were the most common grade 3-4 AEs. Five patients died during the study; these deaths were not attributed to the study drug. The DREAM trial concluded that the combination of durvalumab, cisplatin, and pemetrexed had promising activity and an acceptable safety profile.[78]

The PrECOG LLC study was a phase 2, single arm, multicentre study of durvalumab in combination with cisplatin and pemetrexed for the first-line treatment of unresectable PM.[79] The study enrolled 55 patients with epithelioid (75%), biphasic (11%), sarcomatoid (13%), and desmoplastic (2%) histologic subtypes. The median follow-up was 20.6 months. The median OS was 21.1 months and the 12-month OS rate was 70%. The investigators concluded that the combination of chemotherapy with durvalumab led to OS improvements in the previously untreated patients with unresectable PM.[79]

The open-label, randomized, phase 3 CheckMate 743 trial was conducted in 605 eligible individuals aged ≥18 years with previously untreated, histologically confirmed unresectable PM.[71] The median follow-up was 29.7 months (interquartile range, 26.7-32.9 months) at primary analysis. Treatment with nivolumab+ipilimumab significantly extended the OS when compared with chemotherapy (median OS, 18.1 months vs 14.1 months, HR: 0.74, 96.6% CI, 0.60-0.91). Two-year OS rates were 41% in the nivolumab+ipilimumab group and 27% (95% CI, 21.9-32.4) in the chemotherapy group. Among 300 patients treated with nivolumab+ipilimumab, 30% reported grade 3-4 treatment-related adverse events, whereas these percentages stood at 32% for 284 chemo-treated patients.[71] The 3-year update results of the CheckMate 743 study corroborated the long-term benefits of combined nivolumab+ipilimumab treatment as compared to chemotherapy with no new safety signals.[80] In a subsequent update, 3-year OS rate was reported as 23% in the nivolumab+ipilimumab arm and 15% in the chemotherapy arm. Moreover, 28% of the responders had ongoing response after 3 years (ORR, 44.0%). In an exploratory biomarker analysis of these updated results, the higher score of 4-gene inflammatory signature correlated with the better survival outcome with nivolumab+ipilimumab combination therapy. The post hoc analysis showed that discontinuation of nivolumab+ipilimumab therapy due to treatment-related AEs did not have a negative impact on the long-term results, since 34% of the responders who had a treatment-related AE leading to treatment discontinuation maintained their responses for 3 years after discontinuation.[80] The CheckMate 743 study revealed that nivolumab+ipilimumab provided significant improvements in OS as compared to standard-of-care chemotherapy, supporting the use of this first-in-class regimen.[71] This regimen has been approved in the USA and EU for previously untreated unresectable PM. In addition, based on the CheckMate 743 study results,[71] nivolumab+ipilimumab regimen became a standard regimen for PM, where chemotherapy is the only relevant comparator for nivolumab+ipilimumab as a first-line treatment option. Table 1 summarize the studies related to the first-line treatment.

Table 1
Studies on the first-line treatments of pleural mesothelioma.

Agents (study) (reference)	N	Histology	Phase	Maintenance	Median PFS (mo)	Median OS (mo)
Cisplatin+pemetrexed vs cisplatin (Vogelzang et al.)[72]	222 vs 226	All	3	Yes (~1 years)	-	12.1 vs 9.3
Pemetrexed+cisplatin+bevacizumab vs pemetrexed+cisplatin (MAPS study)[75]	223 vs 225	All	3	Yes (2 years)	9.2 vs 7.3	18.8 vs 16.1
Cisplatin+pemetrexed+durvalumab (DREAM trial)[78]	54	All	2	Yes (1 year)	6.9	18.4
Durvalumab+cisplatin+pemetrexed (PrECOG LLC study)[79]	55	All	2	Yes (~2 years)	-	21.1
Nivolumab+ipilimumab vs pemetrexed chemotherapy+cisplatin or carboplatin (CheckMate 743 study)[71]	303 vs 302	All	3	Yes (2 years)	6.8 vs 7.2	18.1 vs 14.1

OS, overall survival; PFS, progression free survival.

Second- or later-line treatment

There is no standard second-line treatment for PM. Pemetrexed+platinum can be recommended in patients who are not treated with the first-line pemetrexed+platinum. Given the very limited activity of the second-line chemotherapy in patients with PM, after pemetrexed+platinum combination chemotherapy, nivolumab monotherapy or in combination with ipilimumab can be recommended.[71,81] Single agent vinorelbine or gemcitabine also has very limited clinical efficacy according to phase 2 trials. In previously treated patients, second-line chemotherapy options are gemcitabine, vinca alkaloids, anthracyclines, and raltitrexed. Despite these treatments, the prognosis of PM remains relatively poor. The median survival is 12.0-18.8 months for untreated patients and 6.4 months for previously treated patients.[75,82] In a research study conducted in patients with PM who were under vinorelbine or gemcitabine therapies as a second- or third-line treatment, the PFS and OS were found as 1.7 months and 5.4 months in the vinorelbine arm, respectively, and as 1.6 months and 4.9 months in the gemcitabine arm, respectively.[83] However, the absence of a placebo arm and the low response rates were noted in the study.[83] In the randomized, phase 2 Italian RAMES study, the efficacy of gemcitabine with or without ramucirumab as a second-line treatment was investigated on the patients with advanced PM.[84] The study showed a significant improvement in the median OS in the gemcitabine+ramucirumab treatment arm as compared to the gemcitabine+placebo treatment arm (13.8 months vs 7.5 months).[84]

The lack of availability of optimal treatment options has provided a window to test immunotherapies in PM. Inflammatory processes after asbestos exposure and an immunosuppressive TME suggest that patients may benefit from immunotherapies.[85] The reported data on the efficacy of immunotherapy, both as first-line and subsequent-line of treatment, have led to disagreements among clinicians on the selection of patients who will benefit most from immunotherapy and on the sequence of immunotherapy and chemotherapy administrations. The DETERMINE trial is the first salvage immunotherapy clinical trial of a checkpoint inhibitor in PM involving anti-CTLA4 as the second-line therapy.[86] As a single anti-programmed cell death receptor-1 (PD-1)/PD-L1 therapy, pembrolizumab, nivolumab, and avelumab have also been investigated in the salvage settings.[87-91] These trials have shown that the response rate of mono-immunotherapy in salvage treatment is between 20% and 30%, except for avelumab (9.4%) and tremelimumab (4.5%). The open-label 1:1 randomized phase 3 PROMISE-meso trial evaluated the efficacy of pembrolizumab in patients with PM progressing after platinum-based chemotherapy.[92] There was a significant improvement in ORR with pembrolizumab as compared to chemotherapy (22% vs 6%). However, no improvement was observed in the survival rate by pembrolizumab monotherapy over chemotherapy.[92] Another double-blind randomized phase 3 study, the CONFIRM trial, investigated the efficacy of nivolumab versus placebo in patients with unresectable PM progressed after the first- or second-line therapy.[81] Longer OS was observed with nivolumab as compared to placebo (median, 9.2 months vs 6.6 months; hazard ratio [HR]: 0.72; 95% confidence interval [CI], 0.55-0.94; $P = 0.02$).[81]

The NIBIT-MESO-1 single arm phase 2 trial investigated the efficacy of tremelimumab+durvalumab in 40 patients with PM and reported the ORR as 28% and the median PFS and OS as 5.7 months and 16.6 months, respectively.[93] The single arm phase 2 INITIATE trial evaluated the clinical efficacy of nivolumab+ipilimumab in 34 patients with PM and showed that the ORR was 38% and the median PFS was 6.2 months.[94] The open-label phase 2 IFCT-1501 MAPS2 trial compared nivolumab versus nivolumab+ipilimumab in 125 patients with PM.[95] There was an improvement by combination therapy in ORR (28% vs 19%), median PFS (5.6 months vs 4 months), and median OS (15.9 months vs 11.9 months) greater than those observed with monotherapy.[95] These studies have all shown a good safety profile of combination therapy in patients with PM. Besides, it should be borne in mind that the second line therapies that included immunotherapy were only for those patients who had not previously received an immune checkpoint inhibitor. Table 2 shows the clinical trials using monotherapy or combined treatment as a second- or later-line option.

Table 2
Summary of clinical studies using monotherapy or combined treatment as a second- or later-line option in mesothelioma patients.

Agents (study) (reference)	Target molecules inhibition	Line	N	ORR (%)	DCR (%)	Median PFS (mo)	Median OS (mo)
Tremelimumab vs placebo (DETERMINE trial)[86]	CTLA-4	2nd and 3rd line	382 vs 189	4.5 vs 1.1	27.7 vs 21.7	2.8 vs 2.7	7.7 vs 7.3
Pembrolizumab (KEYNOTE-028 trial)[87]	PD-1	2nd line	25	28	76	5.8	18
Pembrolizumab (Desai et al. study)[88]	PD-1	≥3rd line	64	19	66	4.5	11.5
Pembrolizumab (Swiss Registry)[90]	PD-1	Any line	48	25	52	3.2	7.9
Nivolumab (MERIT study)[91]	PD-1	2nd and 3rd line	34	29.4	67.6	6.1	17.3
Avelumab (JAVELIN trial)[89]	PD-L1	Any line	53	9.4	56.6	4.3	-
Pembrolizumab vs chemotherapy (PROMISE-meso trial)[92]	PD-1	2nd line	73 vs 71	22 vs 6	-	2.5 vs 3.4	10.7 vs 12.4
Nivolumab vs placebo (CONFIRM trial)[81]	PD-1	2nd and 3rd line	221 vs 111	-	-	3.0 vs 1.8	9.2 vs 6.6
Tremelimumab+ durvalumab (NIBIT-MESO-1 study)[93]	PD-1+CTLA-4	1st or 2nd line No prior I/O	40	28	65	5.7	16.6
Ipilimumab+ nivolumab (INITIATE trial)[94]	PD-1+CTLA-4	At least 1 prior therapy No prior immunotherapy	34	38	68	6.2	-
Ipilimumab+ nivolumab vs nivolumab (IFCT-1501 MAPS2 trial)[95]	PD-1+CTLA-4	2nd or 3rd line No prior immunotherapy	62 vs 63	28 vs 19	50 vs 44	5.6 vs 4.0	15.9 vs11.9

DCR, disease control rate; IFCT, *Intergroupe Francophone de Cancérologie Thoracique* (French Cooperative Thoracic Intergroup); ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, Programmed death-ligand 1; PFS, progression free survival.

Radiotherapy in PM

Attempts to employ radical radiotherapy in PM have been limited. If pneumonectomy cannot be performed, delivering tumoricidal doses of radiation to the pleura without significant toxicity is difficult in PM cases because of the complex shape of the pleura and dose restrictions. However, several studies have been performed to assess the effect of radiotherapy. Rosenzweig et al.[96] implemented a technique of using intensity-modulated radiotherapy (IMRT) on 36 patients with 2 intact lungs and PM with pleural IMRT to the hemithorax (median dose, 46.8 Gy, range, 41.4-50.4 Gy) and showed that this was a safe and feasible treatment option with an acceptable rate of pneumonitis. In a multicenter, single-arm phase 2 trial, radiotherapy has been concluded as an effective treatment for pain control but ineffective in improving other symptoms or quality of life.[97] In a prospective study, the median OS was reported as 33 months and the 3-year OS rate was reported to be 49% from the long-term results of patients with PM treated with radical pleurectomy/decortication followed by high doses (50 Gy in 25 fractions) of radiotherapy.[98] That study suggested this approach as a concrete therapeutic option for PM.[98] In a study from Turkey, the efficacy and toxicity of the 3-dimensional conformal hemithoracic radiotherapy after EPP were evaluated in 14 patients who received a total median dose of 50.4 Gy to the hemithorax.[99] The median survival was reported as 17.4 months (95% CI, 11-24 months). Radiotherapy was generally well tolerated without major toxicity. The investigators concluded that high-dose adjuvant radiotherapy could decrease the local recurrence rate, particularly after

EPP compared with more limited surgery.[99] In their systematic review of 3 electronic databases and a total of 249 articles, Ashton et al.[100] assessed the feasibility of delivering photon-based, high-dose radiotherapy with radical intent in PM. Although most of the literature were based on data from small cohorts, low quality retrospective studies were inconsistent in radiotherapy techniques and dosimetry; a number of prospective phase 2 studies have suggested that radical doses of radiotherapy can be delivered safely after a lung sparing procedure in PM. Adjuvant radiotherapy can be used for patients with good performance status to decrease loco-regional relapses. However, survival advantage has not been shown with hemithoracic radiotherapy. Palliative radiotherapy is also an effective therapeutic approach for the relief of chest pain, obstructive symptoms, or bone metastases. Use of IMRT is essential after EPP to improve target coverage and spare normal tissues.[101,102] Prophylactic radiotherapy is not routinely recommended to prevent recurrence within intervention sites after biopsy or surgical interventions.[103] Although, the European Society for Radiotherapy and Oncology group has listed the evidence-based recommendations on diagnosis, pathology, staging, monitoring, treatment, and palliative care of PM, the need for detailed guidelines regarding the use of radiation therapy still remain.

Newer agents

Despite the recent introduction of immune checkpoint blockade-based therapies, PM remains fatal in the majority of cases. New promising therapies need to be investigated. Thus, randomized clinical trials which focus on evaluating single agent checkpoint blockade, combining immunotherapies, and combining checkpoint blockade with existing therapies are valuable sources for evidence-based therapies. The role of research would also become more obvious with the latest improvements on biomarker guided targeted therapies.

Oncolytic virotherapy is a new approach with potential in the treatment of PM. Combination of immune checkpoint inhibitors and oncolytic viruses are being tested. Cancer vaccine studies appear to be a promising strategy.[104] Enhancer of zeste homolog 2 (EZH2), which shows pro-oncogenic and immunomodulatory activities in various tumors, has a new target potential promising in the treatment of PM. In the multicenter, phase 2 study by Zauderer et al.,[105] the effect of tazemetostat, a selective oral EZH2 inhibitor, was evaluated in the treatment of relapsed or refractory PM. The disease control rate was reported as 54% (95% CI, 42-67; 33 of 61 patients) at week 12 after a median follow-up of 35.9 weeks.[105] The therapeutic potential of abemaciclib, a CDK4/6 inhibitor, has been evaluated in combination with chemotherapy.[106] Chimeric antigen receptor T-cell therapy has also emerged as a new potential treatment for PM. The tumor-associated antigen mesothelin is considered a target in the treatment of patients with PM as it is expressed at high levels.[107]

Conclusion

Although significant improvements have been made in diagnosis and treatment of many malignancies, therapeutic challenges remain in PM. Multimodality is essential in the treatment and interdisciplinary cooperation is crucial. The surgery selection criteria, lack of effective treatments, unmet need for the first-line regimens, radiotherapy, and use of novel therapies still need to be agreed, highlighting the need for personalized treatment.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Kaplan is on Advisory Boards of Roche, Bristol Myers Squibb (BMS), Merck Sharp & Dohme (MSD), Bayer, Pfizer, and Abdi Ibrahim Ilac and reports honoraria from Roche, BMS, MSD, Bayer, Pfizer, Amgen, Astra Zeneca, Nobel, and Astellas;

all outside the submitted work. Dr. Şendur is on Speaker's Bureau for BMS, MSD, Pfizer, Amgen, Novartis, and Astellas and is on Advisory Boards of Amgen, BMS, MSD, Pfizer, Roche, Novartis, Astellas, and Takeda; all outside the submitted work. Dr. Kayı Cangır has declared no conflict of interest. Dr. Fırat has declared no conflict of interest. Dr. Göker is on Speaker's Bureau for BMS, MSD, Amgen, Pfizer, Novartis, Astra Zeneca, Roche, Jansen Cilag, Takeda, Astellas, and Lilly and is on Advisory Boards of Amgen, BMS, MSD, Pfizer, Novartis, Astra Zeneca, and Roche; all outside the submitted work. Dr. Kılıçkap has declared no conflict of interest. Dr. Oyan reports research support for clinical trials through institution from Novartis and honoraria from BMS, Amgen, Novartis, Pfizer, Astra Zeneca, Roche, and MSD, and is on Advisory Boards of Takeda, Roche, Astra Zeneca, MSD, Novartis, Amgen, and Gilead; all outside the submitted work. Dr. Öz has declared no conflict of interest. Dr. Özdemir has declared no conflict of interest. Dr. Özyiğit has declared no conflict of interest.

Author contributions

All authors made substantial contribution in conceptualization, validation, methodology, writing - original draft preparation, writing—review and editing, resources, visualization, and supervision. All authors read and approved the final manuscript.

Data availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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