Chapter

Immunotherapy in Malignant Pleural Mesothelioma

Asako Matsuda and Nobukazu Fujimoto

Abstract

Malignant pleural mesothelioma (MPM) is an extremely aggressive plural malignancy mainly caused by asbestos exposure. Basic research about the immune suppressive tumor microenvironment in MPM has suggested that MPM might be a good candidate for immune therapy. Immunocheckpoint inhibitors have shown some promising results. A phase Ib trial with pembrolizumab, an antibody specific for the programmed cell death 1 protein (anti-PD-1), showed efficacy in patients with programmed death-ligand 1 (PD-L1)-positive MPM. Among 25 patients tested, 5 patients (20%) achieved a partial response. A Japanese group evaluated the efficacy and safety of nivolumab, an anti-PD-L1 antibody, for patients with advanced MPM in a phase II study. Ten (29%) patients showed an objective response. Based on those results, nivolumab was approved in Japan for unresectable recurrent MPM. A phase III randomized study was conducted to compare nivolumab plus ipilimumab to platinum doublet chemotherapy as a first-line therapy in unresectable MPM. The primary endpoint, overall survival (OS), was significantly improved in the nivolumab plus ipilimumab group. Cellular therapies and cancer vaccines are limited by many challenges; therefore, improvements to overcome these difficulties are urgently warranted. Further research is needed, including large-scale clinical trials, to clarify the utility and safety of immunotherapy in MPM.

Keywords: asbestos, ipilimumab, nivolumab, mesothelioma, pembrolizumab

1. Introduction

Malignant pleural mesothelioma (MPM) is an extremely aggressive plural malignancy, which is mainly caused by asbestos exposure [1]. The benefit of surgical resection is controversial, because only a minority of patients with MPM meets the criteria for surgery, and it is unrealistic to assume that surgery will achieve a complete tumor resection without a micro residual tumor. Systemic chemotherapy with platinum plus pemetrexed is the recommended first-line systemic therapy for advanced MPM. However, the median overall survival (OS) is only approximately 12 months [2]. For patients that fail first-line chemotherapy, a standard second-line chemotherapy has not been defined [3]. Hence, it is critically essential to develop a new treatment option.

Recently, immunocheckpoint inhibitors (ICIs) have achieved great success in treating several cancer types [4–7]. Basic research about the immune-suppressive tumor microenvironment in MPM has suggested that MPM might be a good candidate for immune therapy [8, 9]. CD8+ tumor-infiltrating lymphocytes were

reported to predict a favorable prognosis after a resection of MPM [10]. In fact, recently, ICIs have shown promising results for patients with MPM.

In this chapter, we summarize recent studies on immunotherapy for MPM.

2. Anti-cytotoxic T-lymphocyte antigen 4 antibody

Anti-cytotoxic T-lymphoctye antigen 4 (CTLA-4) antibody was the first reported ICI for treating MPM. To date, three clinical trials have tested anti CTLA 4 antibody monotherapy for MPM.

In the first phase II trial (MESOT-TREM-2008), the anti-CTLA-4 monoclonal antibody, tremelimumab (15 mg/kg) was administered intravenously once every 90 days to patients with MPM [11]. Twenty-nine patients with MPM that had failed a first-line platinum-based regimen were enrolled. Of these, no patients achieved a complete response, 2 patients achieved a partial response, and 7 others achieved durable disease control. The median progression-free survival (PFS) was 6.2 months, and the median OS was 10.7 months. The second phase II trial (MESOT-TREM-2012), enrolled 29 patients with MPM that were treated with 10 mg/kg tremelimumab, initially every 4 weeks for 6 doses, then every 12 weeks [12]. The disease control rate was slightly improved after this regimen modification; one patient achieved a partial response, and 11 patients achieved disease control.

Based on these two trials, a large scale, randomized trial (DETERMINE) was conducted [13] with 571 patients with MPM. Of these, 382 patients were assigned to tremelimumab and 189 patients were assigned to placebo. However, there was no significant difference in PFS or OS between these two groups. After the DETERMINE trial, anti-CTLA-4 antibodies were investigated only in combination with an anti-programmed cell death protein 1 (anti-PD-1) antibody or anti-programmed death ligand 1 (PD-L1) antibody.

3. Anti-PD-L1 antibody

Mansfield et al. reported that PD-L1 was expressed in approximately 42 of 106 MPM specimens, and that PD-L1 expression was significantly correlated with poor survival (OS: 5 months in a PD-L1-positive group vs. 14.5 months in a PD-L1-negative group) [14]. Cedrés et al. also reported that PD-L1 expression was a negative prognostic factor in patients with MPM [15]. These results supported the notion that PD-L1 might serve as a potential target for immunotherapy in MPM.

Avelumab is a human IgG1 monoclonal antibody that binds to PD-L1 [16]. Hassan et al. described a phase I trial (JAVELIN Solid Tumor) that enrolled 53 patients with unresectable MPM. Those patients had failed first-line chemotherapy with platinum and pemetrexed. When they were treated with avelumab, the objective response rate was 9% (one complete response and four partial responses) [17]. Responses were durable (median, 15.2 months), and they were observed both in patients with PD-L1-positive tumors (objective response rate [ORR]: 19%) and in those with PD-L1-negative tumors (ORR: 7%). The median PFS was 4.1 months, and median OS was 10.7 months.

Another anti-PD-L1 antibody, durvalumab, was recently evaluated for efficacy in 54 patients with MPM that were not treated previously. Durvalumab was combined with cisplatin and pemetrexed as a first-line chemotherapy (DREAM trial) [18]. The ORR was 48%, and, 31/54 (57%) patients were progression-free at 6 months. Based on the phase II trial results, a phase III trial is currently planned.

4. Anti-PD-1 antibody

4.1 Pembrolizumab

Pembrolizumab is an antibody against PD-1. Pembrolizumab was tested for efficacy in 25 patients with PD-L1-positive MPM in a non-randomized, phase Ib trial [19]. Five patients (20%) achieved a partial response, and 72% of patients achieved disease control. The median OS was 18 months.

A phase II trial of pembrolizumab monotherapy was conducted in 65 patients with MPM that had been treated previously [20]. Among those patients, 19% achieved a partial response to pembrolizumab. The median PFS and OS were 4.5 and 11.5 months, respectively.

Based on these two trials, pembrolizumab was administered, off-label, to 93 patients with MPM in Switzerland and Australia [21]. The ORR was 18%, and the median PFS and OS were 3.1 months and 7.2 months, respectively. Patients with high PD-L1 expression showed improved ORR (44%) and PFS (6.2 months). Recently, a retrospective study from Australia analyzed data from patients with MPM that received pembrolizumab as the first-, second-, or subsequent-line treatment. They found an ORR of 18%, and a disease control rate of 56%. The median PFS was 4.8 months, and the median OS was 9.5 months [22].

4.2 Nivolumab

Nivolumab is a fully humanized monoclonal anti-PD-1 antibody. It was first tested in 34 patients with recurrent MPM in the Netherlands [23]. In that single-center trial, patients with MPM received 3 mg/kg intravenous nivolumab every 2 weeks. Among 34 patients, 8 patients (24%) achieved a partial response, and another 8 patients (24%) displayed stable disease at 12 weeks.

A Japanese group also evaluated the efficacy and safety of nivolumab in 34 patients with advanced MPM. That study tested nivolumab as a salvage therapy in a single-arm phase II study (MERIT study) [24]. Patients received 240 mg nivolumab intravenously every 2 weeks. Ten (29%) patients showed an objective response. The median duration of the response was 11.1 months, and the disease control rate was 68%. The median PFS and OS were 6.1 and 17.3 months, respectively. Among patients with PD-L1-positive tumors (≥1% expression), the ORR was 40%. Based on those results, nivolumab was approved in Japan for unresectable recurrent MPM.

5. Combination therapy with ICIs

Based on the favorable results obtained with ICI monotherapy, recent investigations tested combination treatments, with an anti-PD-1 or anti-PD-L1 antibody combined with an anti-CTLA-4 antibody. This combination was expected to maximize T-cell activation.

NIBIT-MESO-1 was open-label, non-randomized, phase II trial, in which 40 patients with MPM received at least one dose each of tremelimumab and durvalumab [25]. Eleven patients (28%) displayed an objective response. The median PFS was 5.7 months and the median OS was 16.6 months.

IFCT-1501 MAPS2 was a multicenter, open-label, randomized, phase II trial, in which 108 patients with MPM were randomly assigned to receive intravenous nivolumab or intravenous nivolumab plus ipilimumab. In the intention-to-treat population, 12-week disease control (primary endpoint) was achieved by 25/63

Agent	Year	N	ORR (%)	mPFS (mo)	mOS (mo)	Study type	Reference
Anti-CTLA4							
Tremelimumab	2013	29	7	6.2	10.7	2	Calabro et al. [11]
Tremelimumab	2015	20	3	6.2	11.3	2	Calabro et al. [12]
Tremelimumab	2017	571	5	2.8	7.7	2b	Maio et al. [13]
Anti-PD-L1							
Avelumab	2019	53	9	4.1	10.7	1b	Hassen et al. [17]
Anti-PD-1							
Pembrolizumab	2017	25	20	5.4	18	1b	Alley et al. [19]
Pembrolizumab	2018	65	19	4.5	11.5	2	Desai et al. [20]
Nivolumab	2018	34	24	2.6	11.8	2	Quispel-Janssen et al. [23]
Nivolumab	2018	34	29	6.1	17.3	2	Okada et al. [24]
Combination therapy							
Tremelimumab/Durvalumab	2018	40	28	5.7	16.6	2	Calabro et al. [25]
Nivolumab/Ipilimumab	2019	62	28	5.6	15.9	2	Scherpereel et al. [26]
Nivolumab		63	19	4	11.9		
Nivolumab/Ipilimumab	2019	34	29	6.2	NR	2	Disselhorst et al. [27]
Nivolumab/Ipilimumab	2020	303	40	6.8	18.1	3	Baas et al. [28]

ORR: objective response rate; mPFS: median progression free survival; mo: months; mOS: median overall survival; CTLA: cytotoxic T-lymphocyte antigen; PD-L1: programmed death ligand 1; PD-1: programmed cell death protein 1.

Table 1.
Overview of clinical trials that tested immunocheckpoint inhibitors for malignant pleural mesothelioma.

(40%) patients in the nivolumab group and 32/62 (52%) patients in the combination group [26]. The INITIATE study also evaluated the efficacy of nivolumab combined with ipilimumab in patients with MPM. In that study, among 34 patients included in the efficacy assessment, ten (29%) patients achieved a partial response, and 23 patients (68%) achieved 12 weeks of disease control [27]. Based on these favorable results, a phase III randomized study was conducted to compare nivolumab plus ipilimumab to platinum doublet chemotherapy as a first-line therapy in unresectable MPM. In that study, 303 patients were randomized to nivolumab plus ipilimumab and 302 patients were randomized to platinum doublet chemotherapy. With a minimum follow-up of 22 months, the primary endpoint, OS, was significantly improved with nivolumab plus ipilimumab compared to chemotherapy (median, 18.1 vs. 14.1 months; hazard ratio, 0.74; 95% confidence interval, 0.61–0.89; P = 0.002) [28].

Overview of clinical trials of that tested ICIs for MPM was summarized in **Table 1**.

6. Vaccine

Cancer vaccines have been tested for various cancer types. These vaccines have included tumor lysate, attenuated bacteria, and single or multiple peptides. Wilms tumor 1 (WT-1) is one of the most well investigated cancer antigens. WT-1 was expressed in tumors in 97% of patients with MPM [29]. Galinpepimut-S, a multivalent vaccine against the WT 1 peptide, can activate both CD4+ and CD8+ T-cells [30]. The efficacy and safety of galinpepimut-S was investigated in a phase II trial. The pilot study demonstrated that the median PFS was 7.4 months in the placebo group and 10.1 months in the vaccine group. The median OS was 18.3 months in the placebo group and 22.8 months in the vaccine group. Based on th0se findings, a clinical trial is currently ongoing to investigate a combination treatment of galinpepimut-S plus nivolumab in patients with MPM (with WT-1-positive tumors). Combining cancer vaccines with ICIs might improve the clinical outcome and open a new avenue of therapeutic strategies for MPM.

7. Dendritic cell therapy

Vaccination strategies have been developed that involve dendritic cells (DCs), which are antigen-presenting cells for T-cell activation. The DCs are pulsed with tumor lysate to overcome the shortcomings of autologous DCs. These strategies have shown remarkable anti-tumor activity, with low toxicity, in several cancer types. In the area of MPM, 9 patients received three vaccinations of autologous mature DCs loaded with autologous tumor cell lysate [31]. Among these patients, 3 showed a partial response in the first 8 weeks after the DC vaccination. However, two of those three patients had received chemotherapy before the DC vaccination, which might have influenced the anti-tumor effect. In the next step of treatment, they added cyclophosphamide to increase the anti-tumor activity by inhibiting regulatory T cells [32]. Ten patients with MPM received cyclophosphamide and a vaccination of autologous mature DCs loaded with autologous tumor cell lysate. Of those ten patients, seven lived longer than 24 months, and the mean OS was 37 months.

Obtaining autologous tumor cell lysate is time consuming, because patients have to undergo multiple tumor biopsies. In one study, allogeneic tumor lysate obtained from a tumor cell line was applied to autologous DCs [33]. Nine patients with MPM

were treated with DC vaccinations (autologous DCs pulsed with tumor lysate from five mesothelioma cell lines). Of these, two patients experienced a partial response and all nine patients established disease control. The median OS was longer than 22.8 months. Based on those promising results, an ongoing phase II/III study is currently testing DCs loaded with allogeneic tumor cell lysate as a maintenance therapy after chemotherapy (DENIM trial) [34].

8. Chimeric antigen receptor T-cell therapy

Chimeric antigen receptor (CAR) T-cells can be used to target specific tumor antigens directly. CAR T-cell therapy has shown clinical efficacy for hematological malignancies, and it was approved by the United States Food and Drug Administration for B cell acute leukemia and diffuse large B-cell lymphoma. Several clinical trials are ongoing to test CAR T-cell therapy on both hematological malignancies and solid tumors [35]. CAR T-cells that targeted WT-1, fibroblast activation protein (FAP), or mesothelin (MSLN) were tested in a clinical trial on MPM. Hass et al. reported the results of a clinical trial for testing CAR T-cells that targeted MSLN on 15 patients with MPM. The CAR T-cells were applied as a monotherapy or in combination with low-dose cyclophosphamide, for solid tumors [36]. The best overall response was stable disease (11 of 15 patients). Currently, several phase I trials are ongoing to examine the efficacy of CAR T-cell therapy in solid tumors, including MPM.

9. Conclusion

The prognosis of MPM remains poor. A PD-1/PD-L1 blockade is an effective treatment option for MPM. The combination of nivolumab (anti-PD-1 antibody) and ipilimumab (anti-CTLA-4 antibody) could be a standard first-line treatment. Additionally, the combination of an ICI with conventional chemotherapy might be a promising treatment option. Cellular therapies and cancer vaccines must overcome many challenges, such as T-cell migration to the tumor and infiltration into the tumor. Improvements in cancer therapies are urgently needed to overcome these difficulties. Further research with large-scale clinical trials are needed to clarify the utility and safety of these immunotherapies in MPM. In addition, in this new era of precision medicine, we need to develop biomarkers to identify which patients would benefit from ICI-ICI combinations, ICI plus chemotherapy, or cellular therapy.

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Conflict of interest

Dr. Fujimoto received consultancy fees from Boehringer Ingelheim, Ono, Bristol-Myers Squibb, Kyorin, and Kissei. Dr. Fujimoto also received honoraria or research funding from Hisamitsu, Chugai, Ono, Taiho, Boehringer Ingelheim, Bristol-Myers Squibb, Novartis, GlaxoSmithKline, and MSD.

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