Chapter

Recent Advances in Systemic Therapy for Malignant Pleural Mesothelioma: Focus on Anti-Angiogenic Inhibitors and Immune Checkpoint Inhibitors

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Abstract

Malignant pleural mesothelioma (MPM) is a neoplasm strongly associated with past exposure to asbestos. In general, the prognosis of patients with MPM is poor; however, in recent years, some encouraging results have been reported for systemic therapies for MPM. In a randomized phase III study, the combination of nivolumab and ipilimumab improved overall survival, compared to the standard platinum-based chemotherapy. An important clinical issue is whether the outcome of patients with MPM might be further improved by combining immunotherapies with cytotoxic chemotherapy and/or angiogenesis inhibitors. This chapter covers recent findings on systemic therapies, including cytotoxic chemotherapy, anti-angiogenic inhibitors, and/or immune checkpoint inhibitors.

Keywords: anti-angiogenic inhibitors, asbestos, immune checkpoint inhibitors, Ipilimumab, nivolumab

1. Introduction

Malignant pleural mesothelioma (MPM) is a rare neoplasm with a poor prognosis. MPM is strongly associated with past exposure to asbestos [1]. Radical surgeries, such as an extrapleural pneumonectomy or pleural decortication, have been performed for treating patients with MPM previously, but favorable results have been observed in only a limited number of patients [2, 3]. Most patients that present with advanced, non-resectable MPM at diagnosis are candidates for systemic treatments. However, systemic chemotherapy can only be administered to patients with good performance status (PS) [4].

In 2003, Vogelzang et al. reported that the combination of pemetrexed and cisplatin (pemetrexed/cisplatin) improved the response rate (RR), progression-free survival (PFS), and overall survival (OS), compared to cisplatin alone [5]. Since then, systemic chemotherapy with platinum and pemetrexed combination has been

considered standard therapy for advanced MPM. However, even with this treatment, the PFS and OS have been estimated at 5.7 months and 12.1 months, respectively [5, 6]. A second-line treatment has not been established. According to the US Surveillance, Epidemiology, and End Results Medicare investigation, the most common second-line treatments are pemetrexed-based retreatment or gemcitabine [6].

There is strong evidence that angiogenesis is an important determinant in the development and progression of MPM. There are two main targets for inhibiting angiogenesis. One is the potent mitogen for endothelial cells, vascular endothelial growth factor (VEGF), which transduces signals by binding to two receptors, VEGF receptors –1 and 2. The other is platelet-derived growth factor (PDGF), which functions as an autocrine growth stimulator in the pathogenesis of MPM [7, 8]. With the introduction of angiogenesis inhibitors, several clinical studies have investigated treatments for MPM.

An alternative approach is to target the complex interaction between cancer and host immunity: cancer cells can acquire the ability to evade the host immune system, which curtails their growth [9, 10]. Cancer cells can also actively subvert the immunosuppressive function of T cells and immune checkpoint molecules, such as cytotoxic T lymphocyte antigen (CTLA)-4, programmed cell death (PD)-1, and PD-ligand (PD-L)-1. In recent years, immune checkpoint inhibitors (ICIs) have shown remarkable results in treating multiple types of neoplasms. The etiology and pathogenesis of MPM are mostly attributed to the generation of an immune microenvironment favorable to tumor growth, caused by asbestos-induced damage [11]. There is evidence that ICIs might play an important role in the treatment of MPM; in fact, some encouraging results have emerged in recent years.

Here, we discuss the results of recent trials on systemic therapies against MPM, with a focus on anti-angiogenic inhibitors and ICIs.

2. Angiogenesis inhibitors

Most early studies on anti-angiogenic agents explored their clinical efficacy as single drugs for treating cancer in the relapsed or recurrent setting. However, the outcome of those studies was generally disappointing. Later, anti-angiogenic agents were combined with cytotoxic agents, mainly pemetrexed/cisplatin.

Bevacizumab is a monoclonal antibody that binds VEGF-A. Bevacizumab was tested in combination with the standard-of-care, cisplatin and pemetrexed, as a first-line treatment. An open-label, randomized phase 2/3 study that added bevacizumab to cisplatin and pemetrexed in chemotherapy-naïve patients showed a beneficial effect [12]. In that study, 448 patients were randomized to either pemetrexed/cisplatin with bevacizumab or chemotherapy alone. Patients were treated for up to 6 cycles. OS was statistically prolonged in the bevacizumab arm; the median OS was 18.8 months, versus 16.1 months for chemotherapy alone (HR: 0.77, 95% CI: 0.62–0.95).

Nintedanib is a multi-target angiokinase inhibitor, with activity against the receptors for VEGF (receptors 1, 2, and 3), PDGF, and fibroblast growth factor. A phase II study on patients with MPM showed that the addition of nintedanib to pemetrexed/cisplatin improved PFS (median 9.4 vs. 5.7 months; hazard ratio [HR]: 0.54; 95% CI: 0.33–0.87; p = 0.010). Moreover, the nintedanib arm showed a trend toward improved OS (median 18.3 vs. 14.2 months; HR: 0.77; 95% CI: 0.46–1.29; p = 0.319), compared to placebo. These positive effects were observed in patients with epithelioid histology. However, the findings were not confirmed in the subsequent phase 3 study [13].

Recently, ramucirumab, an anti-VEGF receptor-2 antibody, was tested in a double-blind, placebo-controlled, phase 2 trial for patients with pretreated MPM. In that trial, 161 patients were randomly assigned to gemcitabine (1000 mg/m^2 intravenously, on days 1 and 8 every 3 weeks) or gemcitabine plus ramucirumab (10 mg/kg, intravenously, on day 1 every 3 weeks) [14]. The OS was prolonged in the ramucirumab arm (HR: 0·71, 70% CI: 0·59–0·85; p = 0·028); the median OS was 13·8 months (70% CI: 12·7–14·4) with gemcitabine plus ramucirumab and 7·5 months (70% CI: 6·9–8·9) with gemcitabine plus placebo. Hypertension was more common in the gemcitabine plus ramucirumab group, but no events were related to bleeding.

3. Immune checkpoint inhibitors

Anti-CTLA-4 antibodies include tremelimumab and ipilimumab. Drugs that block PD-(L)-1 include pembrolizumab, nivolumab, durvalumab, and avelumab.

3.1 Nivolumab monotherapy

The MERIT trial was a phase 2, single-phase study that evaluated the safety and efficacy of nivolumab in Japanese patients with advanced or recurrent MPM, who were refractory or intolerant to 1–2 regimens of therapy [15]. In that study, 34 patients received nivolumab (240 mg intravenously) every 2 weeks, until they displayed progressive disease or unacceptable toxicity. The primary endpoint was the objective RR, which was 29.4% (10/34). The median OS and PFS times were 17.3 and 6.1 months, respectively. Among the 34 patients, 11 (32%) experienced grades ≥3 treatment-related adverse events, including 4 patients (12%) with adverse events that led to study treatment discontinuation (2 events of interstitial pneumonia, and 2 events of pneumonitis). Based on those results, nivolumab was approved for patients with MPM that were refractory or intolerant to prior chemotherapy.

The therapeutic efficacy of nivolumab was confirmed in a phase III trial, which demonstrated that single-agent nivolumab provided a significant improvement in both OS and PFS [16]. In that study, 332 adult patients with previously treated, unresectable, histologically confirmed malignant mesothelioma were randomized to nivolumab or placebo. The median OS was immature, but it was significantly prolonged with nivolumab (9.2 vs. 6.6 months; HR: 0.72; 95% CI: 0.55–0.94; p = 0.02). The median PFS was also prolonged with nivolumab compared to placebo (3.0 vs. 1.8 months; HR: 0.62; 95% CI: 0.49–0.78; p < 0.001). Grades 3–4 treatment-related adverse events occurred in 19% of the nivolumab arm and 6.3% of the placebo arm. Treatment discontinuation due to toxicity occurred in 13.1% of the nivolumab arm, versus 2.7% of the placebo arm.

3.2 ICI-ICI combination

The MAPS2 trial was a multicenter randomized, open-label, phase 2 trial that investigated nivolumab plus ipilimumab versus single-agent nivolumab, as a salvage treatment [17]. In the intention-to-treat population, 12-week disease control was achieved by 32 of 62 patients (52%; 95% CI: 39–64) in the nivolumab plus ipilimumab group and 25 of 63 patients (40%; 95% CI: 28–52) in the nivolumab group. Asthenia was among the most frequent grade 3 adverse events (n = 3 [5%] in the combination arm and n = 1 [2%] in the nivolumab arm).

The CheckMate 743 trial was a global, open-label, randomized, phase 3 study that investigated first-line nivolumab plus ipilimumab versus the standard platinum plus pemetrexed chemotherapy [18]. In that study, 605 patients with previously untreated, unresectable MPM were randomly assigned to nivolumab (3 mg/kg intravenously once every 2 weeks) plus ipilimumab (1 mg/kg intravenously once every 6 weeks), administered for up to 2 years, or platinum (cisplatin or carboplatin) plus pemetrexed chemotherapy, administered once every 3 weeks for up to 6 cycles. The primary endpoint was OS. The OS was significantly extended in the nivolumab plus ipilimumab arm, with a median of 18.1 months (95% CI: 16.8–21.4), compared to 14.1 months (95% CI: 12.4–16.2) in the chemotherapy arm. The HR was 0.74 (96.6% CI: 0.60–0.91). The 1-year and 2-year OS rates were, respectively, 68% (95% CI: 62.3–72.8) and 41% (95% CI: 35.1–46.5) in the nivolumab plus ipilimumab arm, and 58% (95% CI: 51.7–63.2) and 27% (95% CI: 21.9–32.4) in the chemotherapy arm. Across most subgroups, OS was more favorable with nivolumab plus ipilimumab compared to chemotherapy. The most frequently reported grade 3 or higher serious treatment-related adverse events were colitis (3%), in the nivolumab plus ipilimumab arm, and anemia (2%) in the chemotherapy arm.

3.3 ICI-chemotherapy combination

The DREAM trial was a multicenter, single-arm, open-label, phase 2 trial conducted in 9 institutions in Australia [19]. In that study, 54 patients received cisplatin, pemetrexed, and durvalumab, in 3-week cycles, for up to 6 cycles. Durvalumab was continued for maintenance for up to 12 months. The primary endpoint was PFS at 6 months. Among 54 patients, 31 (57%; 95% CI: 44–70) were alive and progression-free at 6 months. The most frequent grade 3–4 adverse events were neutropenia (13%), nausea (11%), and anemia (7%). Five patients died during the study treatment, but none of the deaths were attributed to the study treatment.

The efficacy and safety of cisplatin, pemetrexed, and nivolumab were tested as first-line therapy for MPM in a phase II study, called JME-001 [20]. Cisplatin, pemetrexed, and nivolumab were administered intravenously every 3 weeks, for a total of 4 to 6 cycles. Patients that did not progress during the combination phase received maintenance therapy with nivolumab until disease progression or unacceptable toxicity. Among 18 enrolled patients, 14 (77·8%; 95% CI: 52·4–93·6) showed an objective response. Ten (55·6%) patients experienced grade 3 or worse adverse events, including disorders of metabolism or nutrition (33·3%), loss of appetite (27·8%), anemia (16·7%), and hyponatremia (11·1%). No treatment-related deaths occurred.

The efficacy and safety of pembrolizumab in combination with standard pemetrexed and platinum-based chemotherapy is currently being tested as a first-line treatment for MPM in phase II/III randomized study (NCT02784171) and in multicenter, open-label, non-randomized study (NCT04153565). Those results will be disclosed within a couple of years.

4. Future perspectives

Cisplatin plus pemetrexed has been the mainstay of systemic treatment for MPM. A phase III trial of platinum, pemetrexed plus the anti-VEGF inhibitor, bevacizumab, showed favorable results, with prolonged PFS and OS. The National Comprehensive Cancer Network (NCCN) guidelines advocate adding bevacizumab as an option;

Trial (Reference)	Phase	Primary endpoint	Drug	Number of patients	Histology	ORR (%) (CI)	median PFS (months) (CI)	median OS (months) (CI)
First-line								
MAPS [12]	III	OS	cisplatin + pemetrexed + bevacizumab	223	Epi: 179/223 (80%) non-Epi:44/223 (20%)	N.A.	9.2 (8.5–10.5)	18.8 (15.9–22.6)
			cisplatin + pemetrexed	225	Epi: 182/335 (81%) non-Epi:43/335(19%)	N.A.	7.3 (6.7–8.0)	16.1 (14.0–17.9)
Checkmate 743 [18]	III	OS	pembrolizumab	303	Epi: 229/303 (76%) non-Epi: 74/303 (24%)	40 (34.1–45.4)	6.8 (5.6–7.4)	18.1 (16.8–21.4)
			cisplatin + pemetrexed	302	Epi: 227/302 (75%) non-Epi: 75/302 (25%)	43 (37.1–48.5)	7.2 (6.9–8.0)	14.1 (12.4–16.2)
DREAM [19]	IIb	PFS	platinum + pemetrexed + durvalmab	54	Epi: 45/54 (83%) non-Epi: 9/54 (17%)	48 (35–6)	6.9 (5.5–9.0)	18.4 (13.1–24.8)
JME-001 [20]	II	ORR	cisplatin + pemetrexed + nivolumab	18	Epi: 14/18 (78%) non-Epi: 4/18 (22%)	78 (52.4–93.6)	8.0 (5.6–14.1)	20.8
Second-line or later								
MERIT [15]	IIb	ORR	nivolumab	34	Epi: 27 (79%) non-Epi: 7 (21%)	29 (17–46)	6.1 (2.9–9.9)	17.3 (11.5–N.R.)
MAPS2 [17]	III	If disease control was achieved in at least 40%	nivolumab + ipilimumab	62	Epi: 52 (83%) non-Epi: 11 (17%)	28 (16–40)	5.6 (3.1–8.3)	15.9 (10.7–N.R.)
			placebo	63	Epi: 53 (85%) non-Epi:9(15%)	19 (8–29)	4.0 (2.8–5.7)	11.9 (6.7–11.7)
RAMES [14]	II	OS	gemcitabine + ramcirumab	80	Epi: 68/80 (85%) non-Epi: 12 (15%)	6.3 (2–14)	6.4 (5.5–7.6)	13.8 (12.7–14.4)

Trial (Reference)	Phase	Primary endpoint	Drug	Number of patients	Histology	ORR (%) (CI)	median PFS (months) (CI)	median OS (months) (CI)
			gemcitabine	81	Epi: 70/81 (86%) non-Epi:11/81(14%)	10 (4–19)	7.5 (6.9–8.9)	7.5 (6.9–8.9)
CONFIRM [16]	III	PFS OS	nivolumab	221	Epi: 195/221 (88%) non-Epi: 26/221 (12%)	11 (N.A.)	3.0 (2.8–4.1)	10.2 (8.5–12.1)
			placebo	111	Epi: 98/111 (88%) non-Epi: 13/111 (12%)	1 (N.A.)	1.8 (1.4–2.6)	6.9 (5.0–8.0)

ORR: objective response rate; CI: confidence interval; PFS: progression-free survival; OS: overall survival; Epi: epithelioid; N.A.: not available; and DCR: disease control rate.

Table 1.
Recent clinical studies of systemic treatment in malignant pleural mesothelioma.

however, that regimen has not been approved in most countries. In recent years, ICIs have shown remarkable progress in treating MPM. Summaries of the major trials, with a focus on recent trials, are shown in **Table 1**. They include both salvage treatments and first-line treatments. Based on the CheckMate 743 trial results, the ICI-ICI combination of ipilimumab plus nivolumab could be considered a new standard front-line treatment.

Some unresolved problems should be investigated to make further improvements in the outcome of patients with MPM. One is the rapid drop-off in PFS observed among patients that receive ICIs. A recent study on patients with non-small cell lung cancer showed that ipilimumab plus nivolumab combined with 2 cycles of cytotoxic chemotherapy could reduce the rapid drop-offs in both PFS and OS [21]. Those results supported the notion that the ICI-chemotherapy combination should undergo further clinical development. Results are also anticipated from an ongoing trial that is testing a more aggressive strategy, with a combination of platinum, pemetrexed, atezolizumab, and bevacizumab (BEAT-meso, NCT03762018).

5. Conclusion

The results of various clinical trials that examined ICIs and angiogenesis inhibitors have been published in recent years. These trials have demonstrated better treatment options for MPM, but personalized medicine remains in the distant future. Although, MPM is a rare disease, the prognosis remains extremely poor. Therefore, it is necessary to conduct more clinical trials and translational investigations to establish personalized treatment options that can provide the most benefit to individual patients.

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Conflict of interest

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