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Current evidence and future perspectives of immune-checkpoint inhibitors in unresectable malignant pleural mesothelioma

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ABSTRACT

Platinum-based chemotherapy is commonly used as the standard first-line treatment for unresectable malignant pleural mesothelioma (MPM). However, in recent times, immune-checkpoint inhibitors (ICIs) have led to a paradigm shift. Herein, we review relevant literature and ongoing trials of ICIs used as both first-line and salvage therapies. Specifically, in the Japanese single-arm, phase II trial, the MERIT trial, nivolumab, an antiprogrammed cell death 1 (PD-1) antibody showed favorable efficacy when used as a salvage therapy. Currently, multiple ICI monotherapy or combination therapy trials have been conducted, which could provide further evidence. Among available ICIs, the anti-PD-1 antibody is promising for unresectable MPM, despite the limited efficacy of anti-CTLA4 monotherapy. Ongoing studies will further confirm the potential efficacy of ICIs for MPM, as observed across other malignancies. It is also crucial to identify any clinically useful predictive biomarkers that could reveal ICIs with maximal effects in MPM.

INTRODUCTION

With increasing utilization of asbestos, the incidence of mesothelioma is considered to increase worldwide. Asbestos consumption in the USA has rapidly declined over the last 40 years, which has resulted in a considerable decline in mesothelioma incidence.[1] In Japan, the number of deaths had increased from 500 in 1995 to 1550 in 2016. Mesothelioma manifests mainly in the pleura, peritoneum and pericardium, although most commonly in the pleura.[2]

The major role of chronic inflammation and local tumor suppression in tumorigenesis observed in some experimental models led to the investigation of immunotherapy for malignant pleural mesothelioma (MPM).[3] There have been intensive investigations on the efficacy and safety of immune-checkpoint inhibitors (ICIs) in the treatment of unresectable advanced diseases.[4 5] Herein, we highlight relevant study results, as well as designs and concepts of ongoing studies in both first-line and salvage settings.

Known biology

Among approximately 400 different mineral fibers present in nature, six fibers (amphiboles fibers (crocidolite, actinolite, tremolite, anthophyllite and amosite) and serpentine fiber (chrysotile)) are called as 'asbestos'.[6] They are carcinogenic and have been associated with mesothelioma.[6 7] Furthermore, exposure of the chest to therapeutic ionizing radiation, usually performed to treat lymphomas, has been causally linked to mesothelioma, especially in young patients.[8–10]

The accumulation of genetic aberrations can induce malignancies. Recently, The Cancer Genome Atlas program investigated genetic alterations in mesotheliomas using next-generation sequencing (NGS).[11] The results revealed frequent mutations in BAP1, CDKN2A, NF2, TP53, LATS2 and SETD2.[11 12] Recently, a considerably higher number of genetic alterations in mesotheliomas has been detected than that detected by NGS, including point mutations, minute deletions and copy number changes.[13 14] Furthermore, the vast array of genetic alterations in mesothelioma may lead to producing neoantigens, which correlate with the clonal expansion of tumor-infiltrating T lymphocytes.[13 15] These findings suggest that, in contrast to the hypotheses based on NGS studies, mesothelioma may be immunogenic.[15]

Rationale for the development of immunotherapy

A hallmark of cancer is immune evasion, in which the immune system does not mount an effective antitumor response.[16] Programmed cell death 1 (PD-1) is a negative costimulatory receptor expressed primarily on the surface of activated T cells[17 18] and is involved in maintaining peripheral tolerance. The binding of PD-1 to one of its ligands, PD-L1 or PD-L2,

can inhibit a cytotoxic T-cell response.[19 20] Tumors can co-opt this pathway to escape T-cell-induced antitumor activity.[21–23]

The biology of MPM shows significant heterogeneity in both tumor and the microenvironment. Several studies, on T-cell-inhibitory receptors and chemokines, have indicated the prognostic role of lymphocytes and the occurrence of immunosuppression in MPM.[24 25] In a melanoma model, PD-1 blockade increased the proportion of antigen-specific CTLs that recognized melanoma targets by degranulation, suggesting increased recognition efficiency for cognate peptide.[26] The increased frequency and absolute number of antigen-specific CTLs by PD-1 blockade resulted from augmented proliferation, and not decreased apoptosis. These findings have led to the extensive development of agents blocking immunocheckpoints and their clinical investigation in various malignancies including MPM.

Biomarker in the ICI treatment of MPM

Some sensitive and specific immunohistochemistry markers including calretinin and WT1 are used for diagnosing mesothelioma.[4] However, markers for treatment efficiency have not been established. Generally, PD-L1 expression level is used as the representative maker for predicting the efficacy of ICIs. In the ICI monotherapy with the salvage setting in non-squamous cell non-small-cell lung cancer, the PD-L1 expression level affected the survival efficacy,[27] while its influence was weakened when combined with platinum-based chemotherapy in the first-line setting.[28]

In MPM, 20%–70% of the specimens tested are usually PD-L1 positive.[29] Such a wide range can be attributed to several factors. It could be because tumors are heterogeneous in nature.[4] It could be partially attributed to the antibodies used; SP-263 is the most commonly used antibody,[30–32] and the others include clones E1L3N and 28–8.[33] Furthermore, the histological subtype influences its frequency; PD-L1 expression is higher in non-epithelial mesotheliomas.[34] The cut-off levels of PD-L1 positivity vary among trials.[35] Considering that the positive rates were reported from different small studies with a small number of accrued patients, the data may be limited and actual rates of expression have hardly been studied. In addition to this, whether the ICI efficacy is truly dependent on the PD-L1 expression level is still controversial.

ICIs in the first-line settings

The standard treatment for unresectable, advanced malignant mesothelioma is chemotherapy, although with a very poor prognosis.[36] Similar to its use in non-small-cell lung cancer,[37–44] cisplatin (CDDP) and pemetrexed (PEM) combination therapy (CDDP/PEM) approved by the US Food and Drug Administration (FDA) in 2004, is strongly recommended as the first-line treatment for mesothelioma.[45] Moreover, molecularly targeted agents have been developed to augment cytotoxic chemotherapy. For instance, a randomized phase III MAPS study showed that adding bevacizumab to platinum doublets improved survival (HR of overall survival (OS) and progression-free survival (PFS): 0.77 (95% CI: 0.62 to 0.95); p=0.0167 and 0.61 (0.50 to 0.75); p<0.0001, respectively).[46] However, this regimen is yet to be approved by the FDA. A double-blind, randomized, placebo-controlled phase III study, the LUME-Meso trial of CDDP and PEM with or without nintedanib, a multikinase inhibitor for unresectable epithelioid MPM, showed that the primary endpoint, PFS, was not met.[47] Even with such an aggressive chemotherapy, OS for unresectable mesothelioma remains ≤12 months.[48]

Given the limitations in the efficacy of existing cytotoxic chemotherapy in MPM and recent advances in tumor immunology across various malignancies, ICIs have been investigated for the treatment of unresectable mesothelioma. A single-arm, Durvalumab with First-line Chemotherapy in Mesothelioma study examined treatment efficacy after adding durvalumab, a PD-L1 inhibitor, to CPPD/PEM, in 54 patients with untreated, unresectable MPM[49] (table 1). PFS (the primary endpoint) at 6 months was 57%, and the objective response rate (ORR) was 48%, with a median duration of response of 6.5 months. Immune-related adverse events of grade 3 and higher, occurred in eight patients (15%), including lipase elevation (n=1), pancreatitis (n=1) and renal impairment (n=1).

The Canadian Cancer Trials Group has launched a phase II/III study for unresectable MPM, to verify treatment efficacy following the addition of pembrolizumab, a PD-1 antibody, to the standard CPPD/PEM (NCT02784171) (table 2). The use of durvalumab as the first-line immunochemotherapy is also under evaluation, sponsored by PrECOG (NCT02899195). Japanese investigators are also conducting an exploratory phase II trial, using nivolumab combined with the standard CPPD/PEM, in patients with untreated, unresectable MPM.[50] Furthermore, a large-scale, randomized phase III study, the CheckMate 743 study is currently investigating the survival advantage of the nivolumab/ipilimumab combination immunotherapy, versus platinum/PEM, in 606 patients with untreated, unresectable MPM (NCT02899299).

Single-agent ICI therapy in the salvage setting

Although the salvage setting is discussed before advancements in the first-line setting, currently available agents in the salvage setting rarely work in MPM, with a median survival time (MST) of ≤6 months.[51] Vorinostat, a histone deacetylase inhibitor, was proven not to have any survival advantage in a placebo-controlled randomized phase III trial, the VANTAGE-014 trial,[52] without earlier trial result confirmation.

Thus far, four ICIs have been tested as an immunotherapy against relapsed tumors (table 1). A single-center, single-arm phase II study, the NivoMes trial, with single-agent nivolumab, an anti-PD-1 antibody showed that 16 (47%) of the 34 registered patients with recurrent MPM achieved disease control at 12 weeks (8 with

Table 1 Relevant trial results

Trial name	Year	Phase	RCT	Drug	Primary endpoint	No	PS 0–1	No of sarcomatoid histology	ORR	mPFS (mo)	MST (mo)	Pneumonitis*	Ref.
Frontline setting													
DREAM			No	Durvalumab	PFS, OR	54	100%	–	48%	6.9	–	NR	49
Salvage setting													
<Single agent>													
MERIT	2018	2	No	Nivolumab	OR	34	100%	3 (9%)	29%	6.1	17.3	6%	54
NivoMes	2018	2	No	Nivolumab	DCR	34	100%	2 (6%)	24%	2.6	11.8	12%	53
KN-028†,‡	2017	1b	No	Pembrolizumab	Safety	25	100%	2 (8%)	20%	5.4	18	NR	55
Chicago group	2018	2	No	Pembrolizumab	OR	65	100%	5 (8%)	19%	4.5	11.5	3%	56
JAVELIN	2019	1b	No	Avelumab	OR	53	100%	2 (4%)	9%	4.1	10.7	6%	57
Italian group	2013	2	No	Tremelimumab	OR	29	79%	3 (10%)	7%	6.2	10.7	NR	58
Italian group	2015	2	No	Tremelimumab	irOR	29	79%	1 (3%)	3%	–	–	NR	59
DETERMINE	2017	2b	Yes	Tremelimumab	OS	382	99%	22 (6%)	5%	2.8	7.7§	NR	60
				Placebo		189	100%	16 (8%)	1%	2.7	7.3	NR	
<Combination>													
NIBIT-MESO-1¶	2018	2	No	Tremelimumab/durvalumab	irOR	40	100%	2 (5%)	28%	5.7	16.6	NR	30
MAPS2	2019	2	Yes	Nivolumab/ipilimumab	DCR	62	98%	9 (15%)**	28%	5.6	15.9	2%	31
				Nivolumab		63	97%	11 (17%)**	19%	4.0	11.9	2%	
INITIATE	2019	2	No	Nivolumab/ipilimumab	DCR	34	100%	3 (9%)	29%	6.2	NR	NR	32

*Any grade.
†Those with the following conditions were eligible: (1) failed standard therapy and (2) unable to receive standard therapy.
‡Those with PD-L1-positive tumors were registered.
§OS-HR of 0.92 with a 95% CI 0.76 to 1.12.
¶Subjects who refused the first line platinum-based chemotherapy, or those with disease progression after a maximum of one line of platinum-based therapy, were eligible.
**Including biphasic histology.
DCR, disease control rate; DREAM, Durvalumab with First-Line Chemotherapy in Mesothelioma; irOR, immune-related objective response; MST, median survival time; NR, not reported; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; RCT, randomized controlled trial.

Table 2 Ongoing relevant trials

Trial	Country	Phase	RCT	Regimen	Primary endpoint	No of planned pts	PS	Study start date	Registration no
Front-line setting									
Canadian group	Canada	2/3	Yes	Cis-pem±pembrolizumab	OS	126	0–1	07/10/16	NCT02784171
CM743	Global	3	Yes	Nivolumab/ipilimumab versus p-pem	OS	606	0–1	25/10/16	NCT02899299
PrE0505	USA	2	No	Cis-pem/durvalumab	OS	55	0–1	13/06/17	NCT02899195
JME-001	Japan	2	No	Cis-pem/nivolumab	OR	18	0–1	20/01/18	UMIN000030892
Salvage setting									
Confirm	UK	3	Yes	Nivolumab versus placebo	OS	336	0–1	28/03/17	NCT03063450

Cis-pem, cisplatin and pemetrexed; OS, overall survival; p-pem, platinum (cisplatin or carboplatin) and pemetrexed; PS, performance status; pts, patients; RCT, randomized controlled trial.

partial response (PR) and 8 with stable disease (SD)).[53] In this population, PD-L1 expression did not predict treatment responses. A Japanese single-arm phase II study, the MERIT study, also examined the efficacy and safety of nivolumab monotherapy in 34 patients with MPM with a history of prior chemotherapy.[54] The primary endpoint, ORR, was 29% (10/34), which was dependent on tumor PD-L1 expression, with an ORR of 40% and 8% when PD-L1 expression was ≥1% and <1%, respectively. The median PFS and MST were 6.1 and 17.3 months, respectively. Twenty-six patients (76%) experienced treatment-related adverse events (TRAEs). In essence, these results led to the approval of nivolumab in Japan for unresectable recurrent pleural mesothelioma.

A single-agent pembrolizumab, anti-PD-1 antibody trial (KEYNOTE-028) demonstrated that 5/25 (20%) of previously treated patients with MPM achieved PR, while 13 (52%) had SD, with no treatment-related deaths or discontinuations.[55] The Chicago group also conducted a pembrolizumab monotherapy phase II trial in 65 patients with pretreated mesothelioma.[56] Nineteen per cent of the patients achieved PR, without unexpected AEs. The ORR was associated with PD-L1 expression; 7%, 26%, and 31% in patients harboring tumors with PD-L1-expression level of <1%, 1%–49% and ≥50%, respectively. The study also showed a median PFS and OS of 4.5 and 11.5 months, respectively.

With avelumab, a human anti-PD-L1 IgG_1 antibody, a phase Ib monotherapy trial (JAVELIN) was conducted in 53 patients with pretreated malignant mesothelioma.[57] Despite the 9% response in the whole cohort, ORR seemed different, stratified by the PD-L1 expression level in patients with PD-L1-positive (19% (3 of 16)) vs PD-L1-negative tumors (7% (2 of 27)), considering a ≥5% PD-L1 cut-off. The median PFS was 4.1 months, whereas the MST extended to >10 months. Five patients (9%) had grades 3–4 TRAEs, without treatment-related deaths.

Tremelimumab, an anti-CTLA4 antibody, was also evaluated in a salvage setting. In Europe, two single-arm, phase II monotherapy trials showed preliminary efficacy, with an ORR of 3%–7%.[58 59] Following these trials, a randomized phase IIb study, the DETERMINE study, revealed that tremelimumab failed to significantly prolong OS compared with that of placebo, in 571 patients with previously treated malignant mesothelioma. The MST showed no difference between treatment groups, with 7.7 and 7.3 months in the tremelimumab and placebo arms, respectively (HR 0.92, 95% CI 0.76 to 1.12).[60]

ICI combination therapy in salvage settings

Given that enhanced immunogenicity can be achieved by combining PD1 or PDL1 and CTLA4 inhibitors,[3] several studies evaluating the combination of anti-CTLA-4 and anti-PD-[L]1 antibodies have been reported. A phase II study, the NIBIT-MESO-1 trial, investigated an ICI combination of tremelimumab and durvalumab for unresectable mesothelioma.[30] Subjects who had refused first-line platinum-based chemotherapy, or subjects with disease progression after a maximum of one line of platinum-based therapy, were enrolled. Eleven (28%) of 40 patients had an immune-related objective response. The median PFS and MST were 5.7 and 16.6 months, respectively. Baseline tumor PD-L1 expression did not correlate with the immune-related objective response, and seven patients (18%) had grades 3–4 TRAEs.

A combination therapy of nivolumab and ipilimumab, over nivolumab monotherapy, was examined in a randomized phase II trial (IFCT MAPS2).[31] A total of 125 patients with relapsed MPM were allocated to the combination therapy or monotherapy arm. Disease control rate (DCR), set as the primary endpoint, was 50% and 44%, whereas the ORR was 28% and 19%, respectively. As expected, the combination therapy had an increased risk of AE, with grades 3–4 of 26% and 14%, respectively. Three (5%) of 62 combination group patients had toxicities that led to death (hepatitis, encephalitis and acute kidney failure). When restricted to high PD-L1 tumors (>25%), either of

the regimens seemed effective, with ORRs of 63%–71% in the post hoc analyses.

Similar to this MAPS2 trial, a single-arm study, the INITIATE study,[32] evaluated the efficacy of nivolumab and ipilimumab in mesothelioma refractory to at least one line of platinum-based chemotherapy. Of the 34 patients included in efficacy assessment, 10 (29%) attained PR and 13 (38%) attained SD, resulting in a DCR (primary endpoint) of 68%. Despite the smaller-scale, non-randomized design, this study could reproduce the tolerance and efficacy results obtained from the MAPS2 trial. It also showed a relationship between tumor PD-L1 expression and the efficacy of this combination therapy.

Based on the aforementioned completed trials, several MPM trials are either ongoing or being initiated. The most pivotal is the one initiated by Cancer Research UK: a randomized, double blind placebo controlled CONFIRM trial of nivolumab versus placebo in patients with relapsed mesothelioma (NCT03063450). A total of 336 patients will be recruited from 25 institutes in the UK over a 4-year period. All patients will be treated for 12 months, except in situations of progress or withdrawal. It will be intriguing if this reproduces the Japanese MERIT study results.[54]

Overall, anti-PD-1 antibodies exhibited promising results when used alone as a salvage therapy after the first-line chemotherapy.[53–56]

Unresolved, unmet needs for MPM ICI therapy

Compared with clinical trials targeting other malignancies, the majority of prior MPM trials employed 'small-scale' and 'single-arm' designs, and their primary endpoints were set at only ORR or DCR. No clear survival advantage of ICI has been demonstrated through randomized trials. This is mainly because of the extremely small patient population, and mostly exploratory-type trials.[4] However, favorable responses and survival data could be observed across the studies, which are better than historical data. Considering the current limitations of treatment options in the salvage setting, ICI is now a potential rational and medically useful option for patients with unresectable, relapsed MPM, in the absence of any contraindications. Undoubtedly, well-designed randomized trials provide accurate and consistent data (ie, CONFIRM trial (NCT03063450); table 2). The accumulation of forthcoming relevant data through ongoing clinical trials is important for establishing better ICI use in daily practices.

Among toxicities induced by ICIs, pulmonary toxicity has to be properly managed, as it can be one of the most common causes of ICI-related death. The most common lung toxicity observed in patients receiving ICI treatment is pneumonitis.[61] In our review, as shown in table 1, it occurred in 2%–12% of the patients (median; 6%) in all the trials evaluating ICIs. This seemed almost consistent with that observed in other cancers. The patterns of onset and severity may also vary, and MPM often has characteristics of limited reserve in pulmonary function at the baseline. These findings suggest the importance of vigilance and rapid response. Thus, physicians still should recognize that the diagnosis of pneumonitis is particularly challenging and failure to detect and treat pneumonitis in a timely manner could lead to poor clinical outcomes.

Another unmet need is the identification of predictive biomarkers of ICI effects. Compared with other malignancies, progress in mesothelioma biomarker research is limited. Some of the single-arm ICI studies reveal the correlation between responses and higher PD-L1 expression. However, as insufficient survival data were generated, more established outcome data are needed to confirm the value of PD-L1 immunohistochemistry as a predictive biomarker for the OS effect. Recently, the tumor mutational burden (TMB) analysis using the whole exosome sequence has garnered attention in nivolumab therapy.[62] Moreover, in lung cancer, no association between TMB and PD-L1 expression was revealed.[62] Rather, a combination of them would be of value as a predictive biomarker. Nevertheless, only a few precise biomarkers for ICI efficacy assessments seem to exist in MPM clinical trials, besides PD-L1 expression. Further development of new biomarkers is also required for unresectable mesothelioma.

A majority of patients diagnosed with untreated, unresectable mesothelioma exhibit all expected symptoms at the initial presentation, and thus, do not meet the eligibility criteria to participate in clinical trials. Therefore, study results have to be interpreted cautiously, taking into consideration how each of them can be applied per in-care patient, during daily clinical practices.

In the future, more novel immunotherapy results will be made available, which could possibly lead to further drastic changes in unresectable MPM treatment. Our goal is to carefully evaluate any relevant information and deliver better patient treatment.

CONCLUSIONS

MPM prognosis has been poor with the standard platinum chemotherapy. Recently, in the salvage setting, anti-PD-1 antibodies yielded favorable ORR. Nivolumab is approved for use in Japan. Ongoing studies will further confirm the potential efficacy of ICIs for MPM, as observed across other malignancies. It is also crucial to identify any clinically useful predictive biomarkers that could reveal the ICIs with maximal effects in MPM.

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