Pleural Mesothelioma in the Era of Immunotherapy

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ABSTRACT: Over the course of the last decade, immunotherapy has revolutionised the management of a great number of cancer types. The treatment of pleural mesothelioma, a rare and highly aggressive cancer, is also being transformed by immunotherapy. The recent combination of ipilimumab and nivolumab improved overall survival compared with platinum-based chemotherapy, irrespective of the histology, establishing immunotherapy as a front-line standard of care in advanced pleural mesothelioma. Yet, most patients do not derive long-term benefit from any of the available therapies, and we note a significant lack of predictive and prognostic biomarkers. After progressing on first-line therapy, patients have limited therapeutic options, and data are scarce about optimal sequencing. In this perspective, we discuss the current management of pleural mesothelioma, defining what we consider to be the therapeutic sequence based on performance status and tumour histology. We also highlight promising ongoing trials that could further shape the management of this rare disease.

KEYWORDS: Mesothelioma, immunotherapy, chemotherapy, trials, palliative treatment

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Introduction

Pleural mesothelioma (MPM) is a rare cancer which mainly results from asbestos exposure.[1] In spite of societal changes regarding the use of asbestos, its incidence has risen to around 1 per 100 000 due to lag time between exposure and presentation. Most patients are diagnosed with MPM at an unresectable or advanced stage, associated with high mortality rates.[2]

Recently, in the CheckMate 743 trial, the combination of nivolumab and ipilimumab showed improved overall survival compared with standard chemotherapy. This study has challenged the role of platinum-based chemotherapy as standard of care and placed the chemotherapy-sparing regimen as a valid alternative in the first-line MPM setting. After a first line with combination immunotherapy, the question is how to optimise second-line treatment after progression. In this brief perspective, we provide an overview of current therapeutic options, both in the first and second line of treatment, whether starting with chemotherapy or immunotherapy in patients with unresectable pleural mesothelioma. We conclude by discussing novel therapeutic approaches on the horizon in MPM.

Management of Unresectable Pleural Mesothelioma

First line with chemotherapy

For many years, the front-line standard of care was platinum-based chemotherapy. Cisplatin 75 mg/m^2 with or without pemetrexed 500 mg/m^2 was studied in a phase III trial in 2003. The combination of both showed a longer median overall survival (OS: 12.1 months vs 9.3 months).[3] For elderly patients, carboplatin can be an alternative due to its lower renal toxicity.[4,5]

In the phase III MAPS trial, the addition of the antiangiogenic agent bevacizumab 15 mg/kg every 21 days as first-line treatment showed a significant OS (18.8 months vs 16.1 months, $P = 0.0167$) and progression-free survival (PFS) benefit (9.2 months vs 7.3 months).[6]

Maintenance therapy. A few studies have assessed the role of maintenance therapy, with discordant results. Only the phase II NVALT19 study, evaluating gemcitabine maintenance versus best supportive care, showed a significantly longer median PFS in the gemcitabine arm (6.2 months vs 3.2 months, $P < 0.0001$).[7] Neither pemetrexed nor defactinib maintenance showed prolonged median PFS or OS.[8]

Second-line treatment. All of the current second-line studies are based on progression after first-line chemotherapy, as the latter was the only standard of care until the recent results of CheckMate 743.

After first-line chemotherapy, rechallenge with pemetrexed and a platinum agent can be proposed for patients with a 3-month or greater PFS after first-line pemetrexed-based chemotherapy. Patients whose PFS was 12 months or longer appear to derive the most benefit from rechallenge.[9] Recently, the VIM trial, a phase II randomised study comparing weekly oral vinorelbine to best supportive care, showed an improvement in PFS but a poor objective response rate and no overall survival difference.[10] However, no phase III studies have confirmed any benefit. The possible activity of a single chemotherapy and an antiangiogenetic in second line has been assessed in the RAMES study. Patients in this trial were randomised between single-agent gemcitabine on day 1 and 8 of 3 weekly cycles or gemcitabine with ramucirumab 10 mg/kg. Treatments were continued until progression. The trial included 161 patients and found an OS benefit in the ramucirumab group (hazard ratio [HR]: 0.71,

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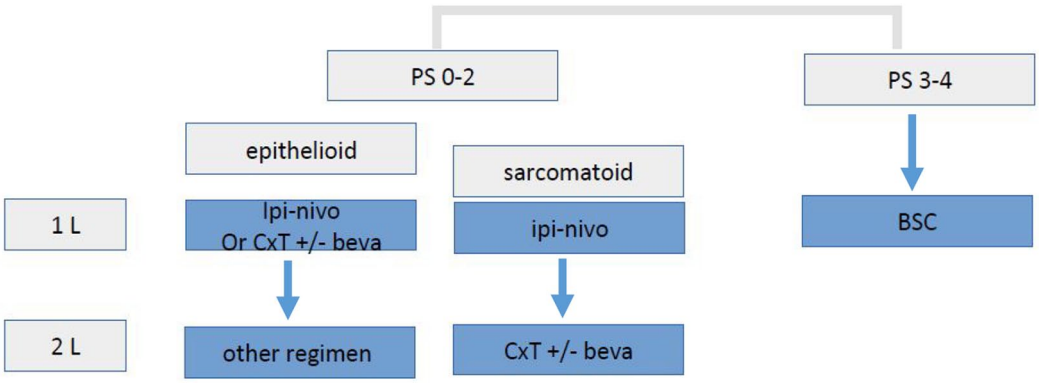

Figure 1. Algorithm for advanced MPM based on histology and performance status.
BSC indicates best supportive care; MPM, pleural mesothelioma; PS, performance status.

70% confidence interval [CI]: 0.59-0.85; $P = 0.028$). The median OS was 13.8 months (70% CI: 12.7-14.4) in the gemcitabine plus ramucirumab group and 7.5 months (6.9-8.9) in the control arm. Despite the positive results, the treatment is not approved in Europe.

Second-line immunotherapy has yielded discordant results. Randomised clinical trials (RCTs) evaluating the effectiveness of immunotherapy in patients with MPM who have progressed after or on previous platinum-based chemotherapy have shown mixed results. For instance, an OS and PFS benefit was reported in the placebo-controlled phase 3 CONFIRM trial, with the anti-programmed cell death-1 (PD1) antibody nivolumab, with a median OS of 10.2 months vs 6.9 months.[11] In contrast, the PROMISE-meso RCT failed to demonstrate PFS and OS benefit when the anti-PD1 antibody pembrolizumab was compared with single-agent chemotherapy, gemcitabine or vinorelbine in second line.[12] Although prognostic and predictive biomarkers would be helpful to select patients with MPM for later treatment lines, there are none currently available. The expression of PD-L1 was neither predictive nor prognostic in the CONFIRM and PROMISE-meso trials.[11,12]

First line with immunotherapy

In 2020, the combination of nivolumab plus ipilimumab was approved by the Food and Drug Administration, based on the results of the randomised phase III CheckMate 743 trial.[13] The immunotherapy combination was compared with platinum doublet chemotherapy and showed significant improvement in OS, confirmed in the recently published 3-year update. With a 3-year follow-up, the median OS is 18.1 months in the immunotherapy arm versus 14.1 (HR: 0.73, 95% CI: 0.61-0.87, $P = 0.002$) months in the chemotherapy arm.[14] In epithelioid subtypes, which represent 75% of cases in this study, a trend for OS benefit was observed but statistical significance was not reached (median OS: 18.2 months vs 16.7 months, HR: 0.85, 95% CI: 0.69-1.04), while non-epithelioid histology was associated with significantly prolonged median OS (18.1 months vs 8.8 months, HR: 0.48, 95% CI: 0.34-0.69). Sarcomatoid subtypes are known to be less responsive to chemotherapy, while they remain sensitive to immunotherapy. The overall median PFS was numerically similar in both arms (6.8 months with immunotherapy arm and 7.2 months with chemotherapy, HR: 0.95, 95% CI: 0.76-1.11). Median OS among patients with a PD-L1 expression of less than 1% was similar in both arms (17.3 months vs 16.6 months, HR: 0.99, 95% CI: 0.69-1.43). Conversely, in patients with PD-L1 expression of 1% or higher, the treatment of nivolumab plus ipilimumab showed a better median OS (18 months vs 13.3 months, HR: 0.69). It should be noted; however, that PD-L1 expression was not a stratification factor. Regarding safety, grade 3-4 adverse events occurred in 30.3% of patients in the experimental arm and 32% of patients in the chemotherapy arm.

Second line after immunotherapy. After first-line immunotherapy, there is no available phase III study data concerning a second line of treatment. At this time, the recommended treatments are those studied in the first line: platinum-based chemotherapy ± bevacizumab, in fit patients. If the patient has poor performance status (Eastern Cooperative Oncology Group performance status 2 or greater), best supportive care is indicated.[15]

Discussion

The CheckMate 743 trial has positioned dual immunotherapy as a valid alternative to chemotherapy as front-line therapy for advanced pleural mesothelioma. When using immunotherapy, the optimal subsequent therapy remains unclear. Furthermore, while the overall survival advantage of combined immunotherapy is evident in non-epithelioid subtypes, in which it is the preferred option, the benefit is less profound in epithelioid subtypes. As such, first-line chemotherapy in combination anti-VEGF antibodies remains a reasonable option to discuss for these patients. The treatment choice will depend on the overall assessment of the patient, including their performance status and comorbidities, patient preferences, and access to drugs (Figure 1). No biomarkers are nowadays available to guide

physician's treatment choice. Many have been explored but none has really been robustly validated in clinical trial.[16]

Modern oncology bases much of the treatment algorithm on predictive biomarkers. In MPM, 4 potential biomarkers have been studied with great interest. The first, PD-L1, is neither predictive nor prognostic in the CONFIRM and PROMISE-meso trials.[11,12] As discussed previously, PD-L1 expression was associated with improved survival outcomes in CheckMate 743, but this was not a stratification factor.[14] The next 3 were assessed in the context of combined immunotherapy in the CheckMate 743 trial. Taking into account the number of somatic missense mutations, patients were classified as low, intermediate, and high tumour mutation burden (TMB) subgroups. TMB was neither predictive nor prognostic and did not influence outcomes with chemotherapy or immunotherapy.[14] It should be noted that the average mutational burden in MPM is low compared with lung cancer, for example.

The next potential biomarker was the Lung immune prognostic index (LIPI) which takes into account the tumour microenvironment and inflammation. It is a composite of the peripheral blood neutrophil-to-lymphocyte ratio (NLR) and lactate dehydrogenase values. While the LIPI score and similar scores are predictive of response in non-small-cell lung cancer, they are only prognostic in MPM and had no predictive use.[14]

Finally, a composite inflammatory signature using an RNA signature for *CD274* (PD-L1), *LAG3*, *STAT-1*, and *CD8A* genes was assessed in CheckMate 743. Classifying patients as having either high or low inflammatory signatures compared with the median of the cohort appears to show an association between inflammation and outcomes on ipilimumab and nivolumab. The 2-year survival was 35% in the higher inflammatory signature half of the cohort and 15% in the lower signature half of the patient population.[14] Nonetheless, this biomarker requires further prospective validation before any clinical implementation.

In addition to the current treatment arsenal, many new therapeutic targets are being studied to personalise patient treatment. Many studies exploring the efficacy of chemotherapy combined with immunotherapy such as DREAM, PrECOG and DREAM3R trials (durva pem platin), BEAT meso (atezo/bev/pem/platin), and the CCTG 227 trial are going to be presented in the upcoming conferences, and they could be potentially practice changing. It will be intriguing to the benefit of chemotherapy and immunotherapy in epithelioid and non-epithelioid mesothelioma opening a scenario where chemotherapy on its own will become obsolete in mesothelioma irrespective of the histological subtypes.

Research has been carried out on the chimeric antigen receptor (CAR) T cells, either intravenously or administered locally (intrathoracic or intraabdominal), given the good encouraging results seen in the treatment of haematological malignancies, such as acute lymphoblastic leukaemia and B-cell lymphomas.[17] Mesothelin is ubiquitous on mesothelial surfaces, particularly in MPM, while rare in healthy tissues, providing a promising target for CAR T cell therapy. Combinations of CAR T cells with chemotherapy or immunotherapy are being investigated in phase I/II trials.[18] Combining PD-1 inhibitors and lymphocyte activation gene-3 (LAG-3) has yielded promising in vitro results and is currently being investigated in clinical trials.[19] Another possible compound which seems to be particularly interesting is lenvatinib, a tyrosine kinase inhibitors (TKI) with preferential antiangiogenic activity. It is being studied in combination with an immune checkpoint inhibitor.[20]

Despite recent advances that have improved the care of patients with MPM, further research is warranted to establish clear therapeutic algorithms, individualise treatment based on predictive biomarkers and improve patients' survival and quality of life (Table 1).

Table 1. Ongoing study.

ONGOING STUDY	PHASE	INTERVENTION/TREATMENT	PRIMARY OUTCOME	SECONDARY OUTCOME	STATUS
Immunotherapy					
NCT04334759	III	Durvalumab with standard chemotherapy vs chemotherapy alone First line	OS	PFS, ORR, QOL	Recruiting
NCT05005429 – BIMES	II	Bintrafusp (M7824)	Efficacy of treatment	ORR, OS, DR	Recruiting
NCT03502746	II	Nivolumab + ramucirumab Previously treated	RR	PFS, OS	Active, not recruiting
PARP-inhibitor					
NCT05455424	II	Niraparib vs active symptom control Previously treated	PFS	OS, BOR, DC, DR, TC	Recruiting

(Continued)

Table 1. (Continued)

ONGOING STUDY	PHASE	INTERVENTION/TREATMENT	PRIMARY OUTCOME	SECONDARY OUTCOME	STATUS
NCT04515836	II	Olaparib in homologous recombination deficiency Previously treated	ORR	OS, PFS	Recruiting
Multi drugs (after molecular pre-screening)					
NCT03654833	II	Rucaparib, abemaciclib, pembrolizumab + bemcentinib, atezolizumab + bevacizumab, dostarlimab + niraparib	DCR	ORR, DCR at 24 weeks, safety and toxicity	Recruiting
Oncoviral therapy					
NCT03710876 – INFINITE	III	Gemcitabine + celecoxib ± rAd-IFN	OS	PFS, BOR, SR	Active, not recruiting
NCT04013334	II	Nivolumab + MTG201 intratumoral inj.	ORR	DR, PFS	Active, not recruiting
Anti-mesothelin					
NCT03126630	I/II	Pembrolizumab ± anetumab ravtansine	TRR	ORR	Active, not recruiting
Dendritic cell vaccination					
NCT03546426 – MESOVAX	Ib	Pembrolizumab + DCV	Safety, PD-L1 expression induction by treatment	Treatment and immunological efficacy	Recruiting
Belderbos et al (39) – DENIM	II/III	Tumour lysate-pulsed DCV + BSC vs BSC	Overall survival rate	/	Recruiting
Synthetic lethal therapies					
NCT02709512 – ATOMIC	II/III	CT ± ADI-PEG 20 or placebo	RR	PFS	Completed (October 2022)

Abbreviations: ADI-PEG20, pegylated arginine deiminase; BOR, best overall response; BSC, best supportive care; CT, chemotherapy; DC, disease control; DCR, disease control rate; DCV, dendritic cell vaccination; DR, duration of response; inj., injection; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; QOL, quality of life; rAd-IFN, adenovirus-delivered interferon alpha-2b; RR, response rate; SR, survival rate; TC, treatment compliance; TRR, tumour response rate.

Author Contributions

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