Chemotherapy options versus "novel" therapies: how should we treat patients with malignant pleural mesothelioma

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Review Article

Chemotherapy options versus "novel" therapies: how should we treat patients with malignant pleural mesothelioma

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Today there are several options for the treatment of patients with malignant pleural mesothelioma (MPM). The therapeutic arsenal has expanded from only chemotherapy with or without surgery in selected cases to a variety of new compounds that target the malignant cell or its micro-environment. Immunotherapy has been the latest achievement and now single arm and randomized studies are being presented. A renewed interest has occurred in the combination of surgery, chemotherapy and radiation therapy. In this review we present the available data on previous and running studies and try to give a recommendation how to select the best patient for the most optimal therapy.

Keywords: Malignant pleural mesothelioma (MPM); systemic treatment; clinical trial; surgery

Submitted Dec 09, 2020. Accepted for publication Jan 16, 2020.
doi: 10.21037/tlcr.2020.01.16
View this article at: http://dx.doi.org/10.21037/tlcr.2020.01.16

Introduction

Until the change of the century patients with malignant pleural mesothelioma (MPM) were treated with best supportive care (BSC) and offered mostly single agent chemotherapy as part of a study. The median overall survival of this group was 7–8 months and only a hand full of chemotherapeutic agents gave responses of 15–20%. One of the most informative studies before 2000 was the MS-01 study from the UK. In this three-arm study, BSC was compared to vinorelbine and to mitomycin plus vinblastine plus cisplatin. No statistical benefit was observed but a slight survival benefit for the vinorelbine arm was noted (1). It was until 2003 that the study by Vogelzang showed a clear benefit from the combination of cisplatin plus pemetrexed versus cisplatin monotherapy. This raised the median overall survival (OS) from 10 to 13 months (2). The combination has been the standard now for over 15 years and is considered the backbone to which other combinations can be tested. The basic idea of the success of this combination is based on the low expression of Thymidilate Synthase (TS) in patients with MPM allowing the multitarget antifolate (pemetrexed) to inhibit the generation of nucleotides in the malignant cells. This, combined with the DNA disrupting effect of cisplatin during the cell division lead to an improved mOS and a response rate of 35% (3).

In this review we describe the literature and latest data and try to recommend the best possible treatment.

Angiogenesis inhibitors

For growth of MPM cells, the vasculature plays an important role. Examination of histologic specimen have indicated that a variety of vascular growth factors play a role. A high micro-vessel count is often seen in patients with active growth of the tumor and are correlated with a worse prognosis. Many receptors have been identified that are activated in patients with MPM, like VEGF-R1 to 4, PDGF and PGF (4-6). Vascular endothelial growth

Table 1 Angiogenesis inhibitors

Inhibitors	Mode of action	Dose	General outcome
Axitinib (9)	VEGFR1–3, PDGFR; c-Kit	5 mg twice daily with CT vs CT	No difference in ORR
Bevacizumab (10-12)	VEGF	15 mg/kg i.v. q 3 wks with CT	mOS 18.8 *vs.* 16.1 HR 0.77 (significant)
Cederanib (13,14)	VEGFR1–3; c-KIT; PDGFRβ	45 mg daily	PR 9–10% significant toxicity
Dovitinib (15)	VEGF; FGF	500 mg daily×5/week	Not active
Nintedanib (16)	VEGFR1–3; PDGFR; FGFR	200 mg twice daily with CT	Phase III study
			PFS: HR 1.01
			OS: HR1.12
Sorafenib CALGB 30307 (17,18)	RAS/RAF/MEK; VEGF; c-KIT	400 mg twice daily	PR 6%
Sunitinib (19,20)	VEGF; c-KIT; PDGF	37.5–50 mg daily	PR 3–12%
			Toxicity when combined with CT
Thalidomide (21)	Inhibits VEGF release and bFGF	200 mg daily	Phase III study
			OS: HR 1.2
Vatalanib (22)	VEFG; PDGF; c-KIT	1,250 mg daily after CT	PR 6%

CT, chemotherapy; HR, hazard ratio.

factor (VEGF) is expressed in MPM, can promote tumor angiogenesis, but also directly stimulate tumor growth (7,8). These observations have led to a variety of studies using anti-angiogenic drugs as shown in *Table 1*. Not only new compounds like small molecules have been tested but also older angiogenic inhibiting drugs like thalidomide. The latter has been tested in a phase III maintenance setting, where patients who did not progress after 4–6 courses of platinum plus pemetrexed, were randomized to receive observation or thalidomide until progression. Although the drug was well tolerated, there was no sign of activity at all compared to observation alone (21). Many phase 2, non-randomized studies have been performed with small molecules directed against the VEGF receptors. Most of these compounds had shown activity in other tumors like kidney cancer. Unfortunately, most of the studies did not show consistent activity in patients with MPM and response rates of 6-12% were noted. The toxicities were often reason for dose reduction or even discontinuation of the therapy. To date no small molecule has been identified to be used on larger scale (9,13-20,22).

A special note must be made for the addition of bevacizumab to the standard of care. In the MAPS study in France, patients were randomized to receive the standard of care with or without bevacizumab in a dose of 15 mg/kg i.v. every 3 weeks. The drug could be given as a maintenance after a maximum of 6 courses of chemotherapy were administered. Two interesting observations could be made in this study; (I) there was a significant mOS benefit for the patients receiving bevacizumab of 2.8 months; (II) the mOS in the control arm had increased to 15 months (10). The latter observation indicates that there may have been a better selection of patients since the SoC reported only a 12–13 months mOS. It remains unclear if this observation is related to the selection for patients fit to receive bevacizumab or that the natural history of the disease has changed in the last 10–15 years. Nowadays, the addition of bevacizumab has been registered as possible new standard of care in some countries.

Maintenance therapies

The use of maintenance therapy has attracted attention in different tumor types and has been tested in patients with MPM. In the first phase III study reported, thalidomide was tested in a dose of 200 mg orally until progression. As stated above, no difference in median progression free survival (PFS) was noted. The mPFS was 3.5 months in both groups with a HR of 0.99 (21). Pemetrexed has been tested as a maintenance drug in a randomized phase II trial. The data

Table 2 Single agent checkpoint inhibitors

Author, trial	Checkpoint inhibitor	Patients (n)	ORR (%)	DCR (%)	PFS (months)	OS (months)
Alley, Keynote028 Phase 1B (28)	Pembrolizumab	25	20	72	5.4	18
Metaxas, Phase II (29)	Pembrolizumab	93	18	48	3.1	7.2
Popat, Promise-meso Phase III (30)	Pembrolizumab *vs.* chemotherapy	73 *vs.* 71	22 *vs.* 6		2.5 *vs.* 3.4	10.7 *vs.* 11.7
Quispel, Nivomes Phase II (31)	Nivolumab	34	26	47	2.6	11.8
Okada, Merit Phase II (32)	Nivolumab	34	29	68	6.1	17.3
Scherpereel, MAPS-2 Phase II (33)	Nivolumab	62	17	43	4.0	11.9
Hassan, Javelin Phase 1B (34)	Avelumab	53	9	47	4.1	10.7
Maio, Determine Phase III (35)	Tremelimumab *vs.* placebo	382 *vs.* 189	4.5 *vs.* 1.1	27.7 *vs.* 21.7	2.8 *vs.* 2.7	7.7 *vs.* 7.3

of this study were presented as poster during ASCO 2019. The study suffered from a very slow accrual and with only 49 patients entered, no difference were observed in both mPFS (3.4 *vs.* 3.0 months) and mOS (16.3 *vs.* 11.4 months P=0.67). The study was stopped for slow accrual (23).

Recently a randomized phase II has been reported during ESMO 2019 with interesting outcomes. In the maintenance setting, gemcitabine was administered in a dose of 1,250 mg/m^2 weekly ×2 every 3 weeks. This regimen was compared to BSC and patients could enroll when no signs of progression were noted after 4–6 courses of platinum-pemetrexed. The drug was well tolerated but a number of patients had dose reductions or change in interval due to toxicity. The primary endpoint was met with an improvement of mPFS of 3 months compared to BSC (3.2 *vs.* 6.2 months). The HR of 0.42 (0.28–6.3) and a P<0.0001 makes this an interesting observation. Eagerly, the mOS data are awaited (24).

Epigenetic interference

Another cell cycle regulatory pathway which attracted interest and is transcription pathway of DNA. In this process, histone deacetylase (HDAC) regulates the timely transcription of DNA by unfolding parts of DNA from the histones. Vorinostat is a HDAC inhibitor with a small molecular weight (<264 g/mol) and leads to induction and accumulation of acetylated histones. This results in a reduction of proliferation of cells, especially tumor cells. This oral medication was tested in second- and third-line treatment in one of the largest phase III studies reported. Despite a positive indication of success in the interim analysis, the final results of 661 randomized patients did not show any difference in mPFS or mOS (30.7 *vs.* 27.1 weeks mOS) (25). It was concluded that single agent HDAC inhibition is not an effective strategy and should probably be combined with other targeted approaches (26).

A more recent development is the observation that the Polycomb Repressor Complex (PRC) is involved in the suppression of tumor suppressor genes in mesothelioma. It was demonstrated that the Enhancer of Zeste Homolog 2 (EZH2) is over-expressed in MPM, and the related PRC-2 is a potential therapeutic target in this tumor. Further studies of TCGA confirmed an up-regulation of EZH2 in MPM cells (27). In order to inhibit the EZH2/PCR2 complex, a drug named tazemetostat has been tested. This compound has now been tested in a small series of 74 patients with MPM, but has not resulted in a full publication (NCT02860286).

Single agent immune checkpoint inhibitors

In the past several years multiple promising data on immune checkpoint inhibitors (ICI) have been reported in the second or later lines (summarized in *Table 2*). Single agent PD-1 ICI have consistent objective response rates of about 20% in mainly phase II trials (28,29,31-34). Single agent CTLA-4 checkpoint inhibitor tremelimumab however did not show any benefit compared to placebo (35).

At ESMO 2019 meeting the PROMISE-meso trial was presented. An ETOP initiated phase III trial with pembrolizumab versus chemotherapy (gemcitabine or vinorelbin) in further lines. Although a significant difference in ORR was seen (22% versus 6%, P=0.004), it did not

Table 3 combination checkpoint inhibitors

Author, trial	Checkpoint inhibitors	Patients (n)	ORR (%)	DCR (%)	PFS (months)	OS (months)
Calabro, Nibit-Meso Phase II (37)	Durvalumab + tremelimumab	40	27	65	5.7	16.6
Disselhorst, Initiate Phase II (36)	Nivolumab + ipilimumab	34	38	68	6.2	NR
Scherpereel, MAPS-2 Phase II (33)	Nivolumab + ipilimumab	63	24	50	5.6	15.9

result in a difference in PFS or OS. The ORR of 22% is consistent with the earlier phase II trials. Treatment related adverse events of grade 3 or higher were experienced in more patients in the chemotherapy group (19% versus 24%) (30). Whether a small subgroup exists that does have a survival advantage for ICI over chemotherapy is not yet known, neither how to select patients that will have a response. In most of the above-mentioned trials, tumors with PD-L1 expression have a higher response-rate to ICI than tumors without PD-L1 expression. But this is not consistent, and also tumors without PD-L1 expression have responses.

Combination of immune checkpoint inhibitors with chemotherapy

In line with the positive effect of combining chemotherapy and an immune checkpoint inhibitor in NSCLC, different phase II and III trials are ongoing, with different combinations (NCT02899195, NCT02784171, NCT03762018).

Combination of immune checkpoint inhibitors

In the last 2 years, three separate phase II trials testing a combination of checkpoint inhibitors were published, one combining durvalumab plus tremelimumab (NIBIT-MESO-1) and two with nivolumab plus ipilimumab (MAPS-2 and INITIATE) (33,36,37). These are summarized in *Table 3*. Response rates between 25% and 38% were seen, which seem a bit higher than from single agent PD-1 inhibitors. Whether this will induce a survival benefit is now being tested in a first line phase III trial randomizing between standard chemotherapy and nivolumab plus ipilimumab (Checkmate 743; NCT02899299). Results are being expected next year. The combination of nivolumab plus ipilimumab is already included in the NCCN guidelines. In line with the single agent ICI, selecting patients for the treatment seems crucial; but a biomarker is not yet found.

Dendritic cell immunotherapy

In dendritic cell immunotherapy autologous monocyte-derived dendritic cells are pulsed with allogenic tumor lysate from five different mesothelioma cell lines and reintroduced into the patient by a vaccination. In the first phase 1 trial 9 patients were treated with this (Mesopher) vaccination, which resulted in a DCR of 100% (38). This led to a randomized phase II/III trial testing maintenance vaccination versus observation after effective first-line chemotherapy. This European study is currently including patients (NCT03610360).

Mesothelin targeted therapy

Mesothelin is a cell surface glycoprotein normally expressed on mesothelial cells, and highly expressed in different cancers, especially in epithelioid mesothelioma. Thereby it is an interesting target for therapy, and different approaches are used over the last two decades (*Figure 1*).

One of the approaches is as a chimeric high-affinity monoclonal antibody (amatuximab), potentially this reduces tumor growth by inhibiting mesothelin binding to the extracellular substrate and by antibody-dependent cellular cytotoxicity. But in a multicenter phase II study, amatuximab in combination with pemetrexed and cisplatin failed to show a difference in PFS over historical controls (39).

Another way to target mesothelin is with immunotoxins. An antibody fragment that targets mesothelin is fused to a bacterial exotoxin payload, and after binding it is internalized by the cell via endocytosis and can induce apoptosis. Two different drugs have been, or are now being tested in clinical trials, SS1P and LMB-100. In SS1P a fragment of Pseudomonas exotoxin A (PE38) is fused. As single agent it has modest efficacy, and problem is induction of rapidly evolving antibodies which neutralize the drug (40). The newer drug LMB-100 has a designed PE (PE24) and is designed to be less immunogenic and thereby less toxic; and is now being tested in clinical trials (NCT03644550, NCT02798536).

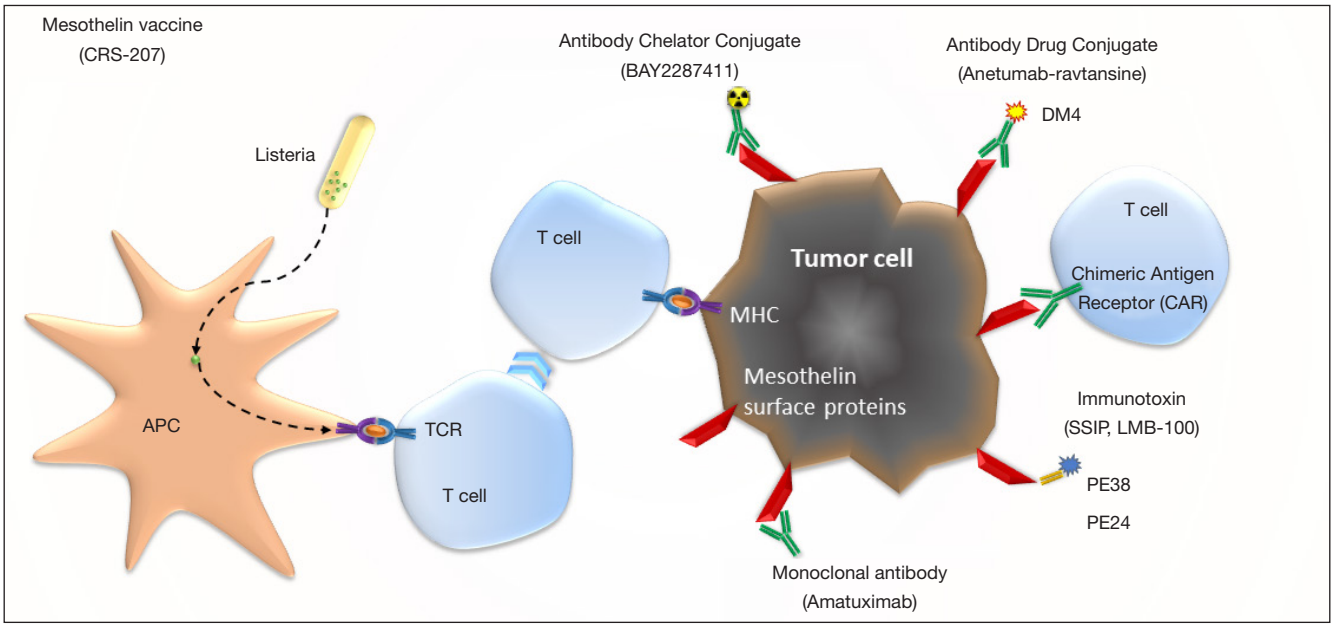

Figure 1 Therapeutics to target mesothelin. APC, antigen presenting cell; MHC, major histocompatibility complex; PE, pseudomonas exotoxin; TCR, T cell receptor. Different mechanisms of targeting mesothelin, a suface glycoprotein.

The third approach is via antibody drug conjugates. Anetumab ravtansine, is an anti-mesothelin antibody fused to DM4, a maytansinoid tubulin inhibitor. After internalization it releases the DM4 metabolite in the tumor cell. In a phase II trial, presented at WCLC 2017, anetumab ravtansine had an objective response of 8.4% and was not superior to vinorelbine with respect to PFS (41). A study randomizing between anetumab ravtansine plus pembrolizumab versus pembrolizumab alone is now recruiting (NCT03126630).

BAY2287411 is a thorium-227-labeled antibody-chelator conjugate, currently being tested in a phase I clinical trial (NCT03507452).

Cancer vaccines are designed to induce a tumor-specific immune response. CRS-207 uses a live-attenuated Listeria monocytogenes strain engineered to express mesothelin. It has been tested in phase I trials, as single agent or in combination with chemotherapy, but although it induces a change in tumor micro-environment and seems to give small benefit, it is no longer tested anymore (42,43). Another cancer vaccine (JNJ-64041757) is also no longer in development.

Over the last two decades many different trials have been performed, unfortunately most without clear effect.

Anti-mesothelin chimeric antigen receptor (CAR) T cells are modified from autologous patient T cells, to express a mesothelin-binding T-cell receptor, and providing antigen specificity to T-cells against tumor associated antigens on the cell surface. Mesothelin CARs are being tested in several trials. A recent phase I basket trial with CAR-T-cells engineered by lentiviral transduction showed it was well tolerated, but showed limited clinical benefit (44). Inefficient T cell infiltration and short persistence by systemic delivery are common obstacles for solid tumor CAR-T cell therapy. Other problems are a cytokine release syndrome and neurotoxicity. Different phase I clinical trials are ongoing (NCT03054298, NCT02414269, NCT03638206).

Arginine deprivation

For the subgroup of sarcomatoid mesothelioma only recently the importance of the arginine succinate synthase (ASS) pathway has been identified (45,46). Using a drug to deplete the body from circulating arginine, the sarcomatoid cells will die due to their inability to endogenously produce arginine. Somewhere during the development of the malignant expression of these cells, there has occurred a loss of the ASS enzyme. In a randomized phase II trial arginine deprivation with ADI-PEG20 improved PFS, but not OS,

over BSC, in patients with ASS1 deficient mesothelioma (47). A phase II/III trial randomizes 386 patients with mixed-type and sarcomatoid mesothelioma, to platinum plus pemetrexed, and either ADI-PEG20 or placebo and is currently recruiting patients (NCT02709512).

Surgery in MPM

The role of surgery in diagnosis and palliation has been well established. In the curative setting, surgery has been performed in patients with MPM for several decades as part of a multi-modality setting. Its primary goal is to eradicate all visible tumor and to allow other modalities to kill the remaining microscopic disease. Different approaches have been investigated, with an Extra-Pleural Pneumonectomy (EPP) being the most radical approach. Several nonrandomized phase II studies showed promising outcomes in highly selected patient groups (48,49). A small but randomized study in the UK (MARS) indicated that toxicity and morbidity was considerable and did not show any signs of improvement (50). The study execution, however, was criticized but gave rise to renewed interest in more limited resections: pleurectomy decortication (P/D). Different ways of performing this resection of all visible tumor with leaving the lung intact have been published. The major problem which is currently under investigation is how the different PD interventions can be compared. In the UK, the MARS2 study investigates the impact of extended pleurectomy/decortication (eP/D) when added to chemotherapy alone (51). The EORTC 1205 study tests the sequence of chemotherapy and eP/D in a randomized study in 64 patients (52). Multimodality treatment is recommended only within clinical trials.

Selection of the best therapy for a patient

In the last years many promising studies with systemic agents have been reported but it all comes down to a long-term benefit in only 20–25% of patients. Despite many investigations, we have not been able to find reliable biomarkers to select for any of the new therapies. It is therefore generally accepted that a platinum with anti-folate combination, potentially including bevacizumab, remains the cornerstone of first-line treatment until a new randomized study beats this standard.

As general recommendation, patients can be selected using the EORTC or CALGB prognostic models for certain (combination) surgical approaches (53) until better biomarkers have been identified.

In further lines no standard therapy is available. Possibilities include chemotherapy (pemetrexed retreatment, gemcitabine or vinorelbine) or immune checkpoint inhibitors (PD-1 +/- CTLA-4). Since ICI have a higher ORR and less toxicity than chemotherapy, possibly this is preferred when available. In the next years several trials with combining agents will be published.

The high expression of mesothelin in epithelioid mesothelioma provides a promising way for use of targeted therapy, but there are still some obstacles to overcome.

We need to continue to encourage patients to enroll in studies to identify which combination of modalities is the most promising and has the least toxicity. It is strongly recommended that these clinical investigations all have strong translational programs.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Disselhorst MJ, Baas P. Chemotherapy options versus "novel" therapies: how should we treat patients with malignant pleural mesothelioma. Transl Lung Cancer Res 2020;9(Suppl 1):S77-S85. doi: 10.21037/tlcr.2020.01.16

