Emerging Drug Therapies for Mesothelioma

Derek B. Oien, Jeremy Chien, Julian Molina and Viji Shridhar

Abstract

The systemic chemotherapy combination of cisplatin and pemetrexed has been the mesothelioma standard of care for well over a decade. This regimen has only achieved a disappointing overall median survival of about 1 year. Improved survival has been reported when systemic chemotherapy is combined with surgery and radiotherapy, and for using localized chemotherapy in some cases. The choice of mesothelioma treatment often depends on the anatomical location, histologic subtype, and disease progression. Several experimental drugs have also been investigated in mesothelioma, often with limited positive results that maintain the reputation of mesothelioma as a graveyard for drug development. This chapter will review the use of drug treatment in mesothelioma and highlight emerging experimental drug therapies in clinical trials. Experimental drugs for mesothelioma include inhibitors for checkpoints, epidermal growth factor, AXL, focal adhesion kinase, vascular endothelial growth factor, poly-ADP-ribose-polymerase, and hippo signaling.

Keywords: targeted drugs, experimental therapeutics, molecular therapies, drug combinations, NF2 mutations, BAP1 mutations

1. Introduction

The treatment of mesothelioma currently varies by primary origin of the tumor, histologic subtype, and disease progression. The most common mesothelioma is malignant pleural mesothelioma (about 80% of cases) [1]. Research for new drug treatments are often investigated in pleural mesothelioma and later extrapolated to less common types such as peritoneal mesothelioma (about 10% of cases). Both of these mesothelioma types have the same three subtypes of epithelioid, sarcomatoid, and biphasic histology. Biphasic mesothelioma is a combination of epithelioid and sarcomatoid histology, each contributing to at least 10% of the tissue [2]. Mesothelioma tends to spread regionally, then into the alternate thoracic lobe for pleural mesothelioma or across the abdomen for peritoneal mesothelioma, and can metastasize across the diaphragm or as distant metastases [2, 3]. Distant metastases were found in a postmortem study in over half of the 318 pleural mesothelioma patients examined, while distant metastasizes of peritoneal mesothelioma are not as common [2, 4]. Surgery is more common when disease is diagnosed early and tumors are resectable, but most patients are diagnosed at later stages of disease when they are not candidates. For pleural mesothelioma, extrapleural pneumonectomy and pleurectomy/decortication are the most common nonpalliative procedures for tumors that are confined to the excised region [5]. Some of these patients...
will be treated with postoperative radiation and systemic chemotherapy, while the benefits of preoperative treatment are still being investigated. For epithelioid peritoneal mesothelioma, cytoreductive surgery is often combined with perioperative chemotherapy [2]. Cytoreductive surgery has been found to have minimal benefit for sarcomatoid and biphasic peritoneal mesothelioma, and systemic chemotherapy is often the first line treatment for these patients [6]. Treatment for relapsed and treatment-refractory mesothelioma is generally palliative or experimental. Currently, there are about 200 initiated and active clinical trials for mesothelioma listed at clinicaltrials.gov (U.S. National Library of Medicine), and the majority of these are drug-based interventions.

There are no targeted therapies currently approved for mesothelioma. Many ongoing research studies and clinical trials are investigating receptor tyrosine kinase inhibitors and checkpoint inhibitors of the immune system. Surprisingly, very few studies are being done that specifically target frequent genetic alterations in mesothelioma. In this review, we discuss the current chemotherapy and highlight emerging experimental drugs for mesothelioma treatment.

2. Systemic and localized chemotherapy

The current chemotherapy standard of care for mesothelioma is a systemic combination of cisplatin and pemetrexed. Adding pemetrexed with cisplatin improved overall median survival of pleural mesothelioma patients from 9.3 months with cisplatin alone to 12.1 months for the combination, which was determined by a phase III clinical trial of the combination in 2003 [7]. Second-line treatments include cisplatin combined with gemcitabine or irinotecan [8–10], and vinorelbine monotherapy [11]. Depending on the disease progression, systemic chemotherapy is often combined with surgery or radiation. The prediction of which late-stage patients will benefit from surgery has proven to be difficult [5]. Radiotherapy alone has not been shown to improve overall survival, but this method is used in combination with surgery or systemic chemotherapy and for palliative purposes. Systemic cisplatin and pemetrexed therapy also remains the standard of care for peritoneal mesothelioma, and this regimen is often used for sarcomatoid and biphasic histologic subtypes [6]. Combining gemcitabine with cisplatin was reported to achieve an overall median survival of about 27 months for patients with unresectable peritoneal mesothelioma, but this combination has also shown considerable toxicity [9]. Similar to several other abdominal cancers, many epithelioid peritoneal mesothelioma patients benefit from intraperitoneal chemotherapy administration.

Cytoreductive surgery followed by perioperative hyperthermic (or heated, hot) intraperitoneal chemotherapy for epithelial peritoneal mesothelioma patients (about 75% of peritoneal mesothelioma patients [2]) has extended overall median survival, which was reported as 53 months [12] and 38 months [13] in two separate multi-institutional studies. The drugs are heated to 42°C and administered to the peritoneal cavity for hours, often while rocking the patient to improve drug dissemination [2]. Intraperitoneal administration of chemotherapy gained attention in the 1980s when this route was shown to have a superior pharmacokinetic profile for cisplatin over intravenous injection in canines [14]. With intraperitoneal administration, most of the chemotherapy remained in the peritoneal cavity and therefore much higher concentrations of drugs could be used, which were up to 30 times greater than common doses for intravenous injection [2, 15]. The effectiveness of hyperthermic intraperitoneal chemotherapy is based on the limits of drug penetration depth and correlates to the ability for achieving complete or near-complete cytoreduction [2, 16]. The drugs used are often varied combinations of cisplatin,
mitomycin-C, and doxorubicin [6]. A significant proportion of patients have also benefited from additional long-term normothermic intraperitoneal chemotherapy following the hyperthermic perioperative dosing [6].

Overall, the main chemotherapy drugs for mesothelioma have led to unsatisfactory overall median survival percentages even when combined with radiation and surgical methods. Many mesothelioma patients try experimental drugs as part of clinical trials or compassionate-use programs. Unfortunately, mesothelioma has gained a reputation as a graveyard for drug development based on the minimal successes and modest extensions of overall survival from experimental drugs. Clinical trials to evaluate targeted drugs in mesothelioma tumors with specific genetic alterations have only recently increased to a relatively small number.

3. Frequent genetic alterations

The most well-known and frequent genetic alterations in mesothelioma are mutations in BAP1, NF2, and TP53 genes and deletion of the CDKN2A gene. These mutations, along with mutations in LATS2 and SETD2, were reported as the most frequent in two independent sequencing studies of mesothelioma tissues [17, 18]. Activation of the LATS2 kinase is regulated by NF2, and the SET2D protein is an H3 histone methyltransferase associated with tumor suppressor activity [19]. While the high frequency of some mutations in mesothelioma have been known for decades (e.g. NF2) and others have been discovered within the last decade (e.g. BAP1), there are still no targeted therapies approved for mesothelioma. Clinical trials requiring genetic testing for inclusion will be discussed in the next section.

Mutations in BAP1, the gene for the BRCA1-associated protein-1 deubiquitinating enzyme, were initially associated with mesothelioma as germline hereditary mutations [20], but it is now estimated that about 60% of mesothelioma tumors contain a mutation in BAP1 (the majority being somatic acquired mutations) [5, 21–23]. It has been demonstrated that BAP1 regulates the DNA repair and apoptotic signaling in response to asbestos exposure [24, 25], which is the most common cause of mesothelioma. BAP1 loss also has been correlated to elevated trimethylation of H3 lysine 27 in mice, which recently lead to targeting the enhancer of zeste homolog 2 (EZH2) methyltransferase as a potential mesothelioma treatment strategy [26]. Germline BAP1 mutations have been found in over 200 families across the globe, and about a third of cancer diagnoses in carriers of BAP1 mutations are types of mesothelioma [5, 27]. BAP1-negative mesothelioma tumors mainly consist of the epithelioid histologic subtype [5].

The most unique frequent mutations for mesothelioma are that of the NF2 gene. The NF2 gene encodes the merlin protein (also known as neurofibromin 2), which has tumor suppressor activity and is associated with cell cycle/growth control through the hippo pathway [28]. Canonical hippo signaling controls the yes-associated protein (YAP), a transcription regulator for many cell cycle-associated genes. Verteporfin is a small molecule with YAP inhibitor activity that is approved for macular degeneration and has recently shown activity against in vitro mesothelioma models [29, 30]. We have found that mesothelioma cells are very sensitive to the antimalarial drug quinacrine in vitro when inactivating NF2 mutations are present (unpublished data). While there are no clinical trials for mesothelioma involving these molecules, both of these drugs have potential to be repurposed for NF2-negative mesothelioma. Outside of mesothelioma, NF2 mutations are only frequently found in a few rare neurological cancers and the inherited neurofibromatosis type II syndrome. It is estimated that about 40% of mesothelioma tumors have NF2 mutations, although there are many other hippo-related genes found mutated in mesothelioma tumors at lower frequencies [31, 32].
Inactivation of the TP53 and CDKN2A genes are not unique to mesothelioma, and these genes are known to be the first- and second-most common mutations in all cancer, respectively. The TP53 gene is only mutated in about 15% of mesothelioma tumors [18], far below the TP53 mutation rate for most other cancer types. Deletion of the CDKN2A gene is found in about 45% of all mesothelioma tumors [18]. The CDKN2A (cyclin-dependent kinase inhibitor 2A) gene encodes for p14arf and p16INK4a tumor suppressor proteins that regulate cell cycle activities.

Mansfield and colleagues recently used mate-pair sequencing analyses to show most mesothelioma tumors contain several chromosomal rearrangements [33]. In 22 mesothelioma patient samples examined, 13 samples contained CDKN2A deletions and 14 samples had NF2 deletions. This suggests the genetics of mesothelioma cancer cells may be altered more than previously detected in several studies that used next generation sequencing methods.

4. Emerging molecular therapies

Pemetrexed was the last drug to be approved by the FDA for mesothelioma in 2004, and now several novel molecular therapies which have had success in other cancers are now being tried in mesothelioma. Among the long list, angiogenesis inhibitors and immune checkpoint inhibitors have arguably made the most progress in clinical trials.

In a recent phase III clinical trial, the vascular endothelial growth factor (VEGF) inhibitor bevacizumab was added to cisplatin and pemetrexed combination therapy for patients with unresectable mesothelioma (Table 1, NCT00651456) [34]. This three-drug combination resulted in significant improvement for overall survival to 18.8 months without a significant negative impact for health-related quality-of-life in patients with advanced pleural mesothelioma [35]. This combination has not yet been approved by the FDA. Another VEGF inhibitor, cediranib, was evaluated in combination with cisplatin and pemetrexed in a phase II trial for unresectable, chemotherapy naïve pleural mesothelioma (NCT01064648). This study reported improved progression-free survival and response rate, but further development has been halted based on the toxicity profile obtained during the trial [36]. Two other multitarget drugs that inhibit VEGF receptors, axitinib and nintedanib, did not meet clinical benefit goals when combined with cisplatin and pemetrexed [37]. Axitinib was unsuccessful when evaluated in a phase II trial for chemotherapy naïve, unresectable epithelioid pleural mesothelioma (NCT01211275). Combining nintedanib with pemetrexed and cisplatin did not meet the primary progression-free survival goals in a phase III clinical trial for advanced pleural mesothelioma [38]. The European-based BEAT-meso phase III trial is in the early stages and adds atezolizumab to the cisplatin, pemetrexed, and bevacizumab combination for advanced pleural mesothelioma (NCT03762018). Atezolizumab is a monoclonal antibody against programmed cell death-ligand 1 (PD-L1). The MiST phase II trial also has an arm for evaluating atezolizumab and bevacizumab in relapsed mesothelioma that has positive PD-L1 expression (NCT03654833). It is estimated that up to 25% of mesothelioma patients may benefit from immune checkpoint inhibitors [5].

Interest in PD-L1 inhibitors for mesothelioma is based on prior success of these inhibitors in other cancer types and a study showing about 40% of the 212 mesothelioma patient samples examined express PD-L1 [17]. It was also shown in the latter study that high PD-L1 expression correlated with poor survival for the mesothelioma patients. In addition to the BEAT-meso clinical trial, atezolizumab is also being evaluated in a phase II trial on unresectable or advanced pleural mesothelioma (NCT03786419). The combination of PD-L1 inhibitor durvalumab with cisplatin
| Study title                                                                 | Drug interventions                              | Phase | NCT number      |
|----------------------------------------------------------------------------|-------------------------------------------------|-------|-----------------|
| Mesothelioma Avastin Plus Pemetrexed-cisplatin Study’                       | Bevacizumab, pemetrexed, cisplatin              | 2/3   | NCT00651456     |
| Pemetrexed Disodium and Cisplatin With or Without Cediranib Maleate in     | Cediranib, pemetrexed, cisplatin                | 2     | NCT01064648     |
| Treating Patients With Malignant Pleural Mesothelioma                       |                                                 |       |                 |
| Standard Chemotherapy With or Without Axitinib in Malignant Mesothelioma    | Axitinib, pemetrexed, cisplatin                 | 2     | NCT01211275     |
| (N08CPA)*                                                                  |                                                 |       |                 |
| Nintedanib (BIBF 1120) in Mesothelioma**                                    | Nintedanib, pemetrexed, cisplatin               | 2/3   | NCT01907100     |
| Bevacizumab and Atezolizumab in Malignant Pleural Mesothelioma (BEAT-meso) | Bevacizumab, atezolizumab, cisplatin, pemetrexed| 3     | NCT03762018     |
| Mesothelioma Stratified Therapy (MiST): A Multi-drug Phase II Trial in     | Bemcentinib & pembrozilumab, atezolizumab &     | 2     | NCT03654833     |
| Malignant Mesothelioma                                                      | pembrazilumab, rucaparib, abemaciclib          |       |                 |
| A Study of Atezolizumab in Unresectable or Advanced Malignant Pleural       | Atezolizumab                                     | 2     | NCT03786419     |
| Mesothelioma                                                                |                                                 |       |                 |
| Pembrolizumab in Patients With Advanced Malignant Pleural Mesothelioma      | Pembrolizumab, pemetrexed, cisplatin            | 2/3   | NCT02784171     |
| CheckpOiNt Blockade For Inhibition of Relapsed Mesothelioma                 | Nivolumab                                        | 3     | NCT03063450     |
| Study of Nivolumab Combined With Iplimumab Versus Pemetrexed and Cisplatin| Nivolumab, ipilimumab, pemetrexed, cisplatin,  | 3     | NCT02899299     |
| or Carboplatin as First Line Therapy in Unresectable Pleural Mesothelioma   | carboplatin                                      |       |                 |
| Randomized, Double-blind Study Comparing Tremelimunab to Placebo With      | Tremelimunab                                     | 2     | NCT01843374     |
| Unresectable Malignant Mesothelioma                                         |                                                 |       |                 |
| A Phase 2 Study of Durvalumab in Combination With Tremelimunab in           | Tremelimunab, durvalumab                         | 2     | NCT03075527     |
| Malignant Mesothelioma’                                                     |                                                 |       |                 |
| Pembrolizumab + Defactinib In Pleural Mesothelioma                          | Pembrolizumab, defactinib                       | 1     | NCT04201145     |
| Targeted Therapy Directed by Genetic Testing in Treating Patients With     | Several targeted drugs including defactinib    | 2     | NCT02465060     |
| Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma (The MATCH| for tumors with NF2 inactivating mutations     |       |                 |
| Screening Trial)                                                            |                                                 |       |                 |
| Everolimus (RAD001) for the Treatment of Malignant Pleural Mesothelioma With| Everolimus                                       | 2     | NCT01024946     |
| Merlin/NF2 Loss as a Biomarker to Predict Sensitivity’                      |                                                 |       |                 |
| Study of the EZH2 Inhibitor Tazemetostat in Malignant Mesothelioma’         | Tazemetostat                                     | 2     | NCT02860286     |
| A Trial of Niraparib in BAP1 and Other DNA Damage Response (DDR) Deficient | Niraparib                                        | 2     | NCT03207347     |
| Neoplasms (UF-STO-ETI-001)                                                  |                                                 |       |                 |
| Olaparib in People With Malignant Mesothelioma                              | Olaparib                                         | 2     | NCT03531840     |
and pemetrexed as a first-line treatment for unresectable pleural mesothelioma has also been reported to be advancing to a larger randomized phase III trial [5, 39]. Pembrolizumab is a PD-1 (which binds to PD-L1) inhibitor currently being used for a phase II/III trial (NCT02784171) for advanced pleural mesothelioma both as a monotherapy (phase II) and in combination with cisplatin and pemetrexed (phase III). Nivolumab is a PD-1 inhibitor in two phase III clinical trials, which are for relapsed mesothelioma (NCT03063450) and as a first-line treatment when combined with ipilimumab for unresectable pleural mesothelioma (NCT02899299). Ipilimumab is a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor that has showed encouraging results when previously combined with nivolumab in two separate phase II trials for mesothelioma [40, 41]. The CTLA-4 inhibitor tremelimumab was reported to be unsuccessful as a second-line treatment in two phase II clinical trials. As a monotherapy, it did not prolong overall survival for both unresectable pleural and peritoneal mesothelioma (NCT01843374) [42] and the primary endpoint for overall response rate was not met when tested in combination with durvalumab for pleural mesothelioma (NCT03075527) [43].

The PD-1 inhibitor pembrolizumab is also being combined with the focal adhesion kinase inhibitor defactinib in a phase 1 clinical trial (NCT04201145). There had previously been a lot of interest in the ability of focal adhesion kinase inhibition to selectively eliminate mesothelioma cells, but enthusiasm significantly decreased after defactinib failed to improve progression-free and overall survival in prior mesothelioma clinical trials (NCT02004028, NCT01870609) [44]. However, defactinib is now also in the MATCH screening phase II trial for patients with advanced refractory solid tumors containing NF2 inactivating mutations as a second-line treatment (NCT02465060, subprotocol U). This is the only current clinical trial (to the best of our knowledge) that may potentially address inactivating NF2 mutations in mesothelioma (note that the trial is not specific to mesothelioma and does not guarantee mesothelioma patient enrollment). The mTOR inhibitor everolimus had been previously studied in a second-line mesothelioma phase II trial that also evaluated NF2 loss as a biomarker of sensitivity (NCT01024946), but this trial resulted in limited clinical activity and everolimus did not progress as a monotherapy agent for mesothelioma [45]. In preclinical studies, we have found that repurposing the antimalarial drug quinacrine may be particularly effective against cells with inactivating NF2 mutations by disrupting hippo signaling (unpublished data). Quinacrine is unique as an anticancer agent in that it has an excellent safety profile from almost a century of use for malaria prophylaxis/treatment [46]. Further mechanistic and clinical studies are needed to fully understand the potential of quinacrine for mesothelioma treatment. Moreover, verteporfin has also been preclinically evaluated as a YAP inhibitor for mesothelioma, but has not progressed to clinical trials yet [29, 30]. To address BAP1 inactivation, a phase II trial testing the EZH2 inhibitor tazemetostat with relapsed/refractory mesothelioma patients as a monotherapy (NCT02860286) recently concluded with encouraging preliminary data, specifically

| Study title | Drug interventions | Phase | NCT number |
|-------------|-------------------|-------|------------|
| Anti-Mesothelin Immunotoxin LMB-100 Followed by Pembrolizumab in Malignant Mesothelioma | LMB-100, Pembrolizumab | 2 | NCT03644550 |

Table 1. Highlighted drug-based clinical trials for mesothelioma from clinicaltrials.gov (U.S. National Library of Medicine).
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benefiting long-term disease control [47]. Targeting BAP1-mutated mesothelioma tumors with poly-ADP-ribose-polymerase (PARP) inhibitors has been promising based on preclinical studies [48, 49]. The PARP inhibitor niraparib is being evaluated as a second-line treatment in a phase II trial for tumors with DNA damage response mutations including BAP1 (NCT03207347). More recently, a phase II trial to evaluate the PARP inhibitor olaparib as a second-line treatment specifically for mesothelioma has started with arms to include BAP1 somatic mutations and germline DNA damage repair mutations (NCT03531840). The MiST phase II trial also has an arm for investigating the PARP inhibitor rucaparib in BRCA1/BAP1-negative mesothelioma patients. Furthermore, the MiST trial has a third arm to study the CDK4/6 inhibitor abemaciclib for mesothelioma patients with p16INK4A negative (CDKN2A deletion) tumors. The fourth MiST arm evaluates AXL inhibitor bemcentinib in combination with pembrolizumab for relapsed mesothelioma patients without specific biomarker requirements. We have previously shown that AXL has relatively high expression in pleural mesothelioma compared to other cancer types, and that bemcentinib can selectively kill mesothelioma cells [50]. In pleural mesothelioma, a phase II trial with epidermal growth factor receptor (EGFR) inhibitor gefitinib was not successful [51]. However, peritoneal mesothelioma often has higher EGFR expression compared to pleural mesothelioma and may benefit from EGFR inhibitor therapy pending more clinical studies that are specific for this indication [2, 52].

Mesothelin and other biomarkers of mesothelioma have gained recent interest as targets for immunotoxins and chimeric antigen receptor-T (CAR-T) cells. Mesothelin has been used for diagnostic purposes in algorithms with other biomarkers as well as occasionally used for tumor surveillance [2, 5]. As a therapy target, the immunotoxin LMB-100 has been recently developed to bind mesothelin [53]. In 2018, a phase II trial started with LMB-100 followed by pembrolizumab for pleural and peritoneal mesothelioma cohorts (NCT03644550). CAR-T cells are also being developed to target mesothelin as a potential mesothelioma treatment [54].

5. Conclusions

Most mesothelioma patients have chemotherapy or experimental drugs as a major part of their treatment plan, but there have been very few highlights and minimal significant advancements for mesothelioma drugs over the last couple decades. Targeting specific types and characteristics of mesothelioma may have the most potential in the near future. It is surprising that targeted drugs as a whole have not progressed to end stages already either because of slower development pipelines or failure to hit endpoints for mesothelioma. There may also be an orphan drug clout that prevents development of drugs to target tumors with BAP1 and NF2 mutations. Proteomic characteristics of mesothelioma, specifically biomarkers currently used for diagnostic and tumor surveillance purposes, may also prove useful for novel chimeric therapies (e.g. protac and chimeric antigen receptor T cells), which are currently being developed for mesothelin. These and emerging targeted drugs such as AXL inhibitors, EGFR inhibitors for peritoneal mesothelioma, PARP inhibitors for BAP1-mutated tumors, and quinacrine for NF2-mutated tumors all have potential to finally kill the reputation of mesothelioma as a drug development graveyard.

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Conflict of interest

The authors have no conflicts of interest to declare.

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