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Chemotherapy and Targeted Therapies for Unresectable Malignant Mesothelioma

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Abstract

The global burden of mesothelioma is expected to increase in the coming decades. As a result the development of more effective therapies with an emphasis on personalized treatments based on validated prognostic and predictive biomarkers is an essential requirement. Progress has been made in the last decade with the development of newer generation anti-folates leading to the current standard of care of pemetrexed and cisplatin in patients with unresectable disease. However, the median overall survival of patients with this combination treatment is only 12 months. There is no consensus regarding second line therapy for patients who have progressed or not responded to pemetrexed based therapies although gemcitabine in combination with a platinum compound or single agent vinorelbine is a reasonable option. The development of effective targeted agents that are active in mesothelioma has to date been disappointing. Strategies involving the addition of bevacizumab to pemetrexed and cisplatin in the frontline setting, the histone deacetylase inhibitor vorinostat as second line therapy and studies evaluating the utility of maintenance therapy in mesothelioma.are all ongoing and appear promising. In addition clinical trials investigating immunotherapy and gene therapy in combination with chemotherapy could potentially improve the prognosis of patients with mesothelioma.

Keywords

mesothelioma; chemotherapy; targeted therapy; immunotherapy; MORAb-009; SS1P

1. Introduction

Malignant mesothelioma is an aggressive neoplasm arising from the mesothelial surfaces of the pleural and peritoneal cavities. It can also develop from the serosal surfaces of the pericardium, or the tunica vaginalis. Up to 80% of all cases are pleural in origin and are defined as malignant pleural mesotheliomas (MPM). Few common cancers have such a direct causal relationship with an exposure to a defined carcinogen as mesothelioma has with asbestos exposure. In 1960 the first convincing evidence of a link between malignant mesothelioma and both occupational and incidental asbestos exposure was reported, on the basis of data from South Africa [1]. The tumor was once considered rare but the incidence worldwide of MPM is anticipated to increase over the next 10 years [2]. The prognosis is worse in male patients and in patients with extensive disease, poor performance status,

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elevated white-cell counts, anemia, thrombocytosis, sarcomatoid histologic findings, or high standardized uptake value ratios on Positron Emission Tomography (PET) [3–4]. Mesothelioma has an unusual molecular pathology with the loss of tumor suppressor genes being the predominant pattern of lesions, especially the $P16^{INK4\alpha}$, $P14^{ARF}$, and NF2 genes, rather than the more common p53 and Rb tumor suppressor genes [5–7]. The role of aggressive surgery remains controversial; however, sufficiently robust evidence to substantiate the use of chemotherapy has emerged in the last 5 years. This paper will summarize the evidence supporting the clinical activity of chemotherapy and discusses the use of second-line therapies including the use of novel agents and immunotherapies, which are currently being evaluated in Phase I/II and III clinical studies.

2. Patients and methods

2.1. CHEMOTHERAPY

2.1.1. Pemetrexed and cisplatin/carboplatin—Prior to 2003, there was no standard chemotherapy regimen for the treatment of patients with unresectable MPM. Two meta-analyses have summarized the available evidence to identify the most active chemotherapeutic drugs and regimens for MPM [8–9]. A number of conclusions can be drawn. Most single agents, with the exception of cisplatin, have low intrinsic activity. The response and survival rates are greater for combination rather than single agent treatments [8–9]. Platinum containing regimens have a greater activity than non-platinum containing combinations. Three drug-containing regimens are no more active than two drug combinations. Randomized trials using newer agents such as pemetrexed and raltitrexed have provided evidence suggesting that a platinum-based doublet containing a third-generation antifolate is superior to using platinum alone [10–11].

Pemetrexed is a novel multitargeted antifolate that inhibits dihydrofolate reductase, thymidylate synthase, and glycinamide ribonucleotide formyl transferase. These enzymes are involved in purine and pyrimidine synthesis [12–13]. A critical step in the *de novo* pathway of DNA synthesis is the production of thymidine monophosphate from deoxyuridine monophosphate. This reaction is catalyzed by thymidylate synthase. Pemetrexed enters the cell via the reduced folate carrier and undergoes extensive intracellular polyglutamation, which leads to a 100-fold increase in the drug's affinity for thymidylate synthase and prolonged concentration of the drug in the cell [14–15]. Raltitrexed is a quinazoline folate analog that acts as a specific thymidylate synthase inhibitor. It also is converted into a polyglutamate form which ultimately increases both its potency and duration of activity.

Vogelzang *et al* performed a Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with MPM [10]. A total of 456 chemotherapynaïve patients who were not eligible for curative surgery were enrolled. The combination regimen had a 41.3% response rate versus 16.7% (P<.0001), median time to progression of 5.7 months versus 3.9 months (P=.001), and a median overall survival of 12.1 months versus 9.3 months (P=.020) in favor of the platinum-based doublet. This study established the combination of cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) every 3 weeks as the new standard of care. The European Organization of the Research and Treatment of Cancer (EORTC) conducted a Phase III study involving 250 treatment naïve patients with advanced MPM with either cisplatin (80 mg/m^2) or the combination of cisplatin and raltitrexed (3 mg/m^2) [11]. The overall response rate was 23.6% versus 13.6% in favor of the combination (P=.056) and the median overall survival was increased to 11.4 months versus 8.8 months in the cisplatin/raltitrexed arm (P=.048). Similar to the results observed in the Vogelzang study this randomized phase III study demonstrated that the combination of cisplatin with an antifolate improved overall survival compared to cisplatin alone. Since raltitrexed is not

commercially available in the United States, the combination of cisplatin plus pemetrexed is currently the standard of care for treating patients with unresectable pleural mesothelioma outside the context of a clinical trial.

The question of whether carboplatin could be substituted for cisplatin was evaluated in the International Extended Access Program (EAP) [16]. This was a multicenter, nonrandomized, open-label study in chemotherapy-naïve patients who received either pemetrexed plus cisplatin (n=843) or pemetrexed plus carboplatin (n=861). Evaluable patients treated with pemetrexed plus cisplatin or pemetrexed plus carboplatin achieved overall response rates of 26.3% and 21.7%, respectively and had comparable median time to disease progression of 7 months versus 6.9 months and similar 1 year survival rates of 63.1% versus 64.0%. Other Phase I and II studies have demonstrated efficacy with pemetrexed plus carboplatin in MPM with response rates ranging from 19–22% and median survival ranging from 13–15 months [17–18]. Although the combination of cisplatin plus pemetrexed is the preferred regimen, in patients for whom cisplatin is contraindicated, substituting carboplatin is a viable alternative.

The role of maintenance pemetrexed after six cycles of frontline chemotherapy remains undetermined and is not considered standard of care at present. The ongoing CALGB 30901 trial is a multicenter randomized phase II study with the primary objective of determining if maintenance therapy with pemetrexed improves the PFS of patients with MPM after completion of upfront therapy comprising pemetrexed with cisplatin or carboplatin. Up to 96 patients are expected to enroll in the two arms of this trial. After completing four cycles of frontline treatment patients who have had a response or have stable disease will be randomized. In arm one, patients receive pemetrexed on day 1 repeated every 21 days in the absence of disease progression or unacceptable toxicity compared to the second arm which consists of observation only until disease progression. If maintenance pemetrexed does improve the PFS, then the benefits of maintenance therapy on overall survival need to be demonstrated since improvements in PFS may not translate into overall survival. In addition, patients who progress after initial treatment with cisplatin and pemetrexed may also benefit from retreatment with pemetrexed at time of relapse[19].

Personalized medicine and the search for predictive and prognostic biomarkers in order to define optimal treatment regimens represent an important challenge in the treatment of MPM. Approximately one half of patients will not respond to front line platinum and pemetrexed combinations. Recent studies have evaluated excision repair-cross complementing group-1 (ERCC1) and thymidylate synthase (TS) as markers to predict clinical outcomes. In a retrospective study, sixty patients with MPM who had previously been treated with pemetrexed and a platinum compound or single agent pemetrexed alone had baseline TS and ERCC1 gene expression levels evaluated by real-time PCR and IHC and compared to a control group of 81 patients not treated with pemetrexed[20]. In patients previously treated with pemetrexed, low TS protein levels were predictive of an improved TTP (17.9m v 7.9m, P=0.02) and a longer median OS (30m v 16.7m, P=0.035). Conversely, there was no significant correlation between TS expression and outcome for patients who were not treated with pemetrexed. In the patients who received a platinum compound, no correlation was found between survival and ERCC1 expression. In a second retrospective trial of MPM patients treated with carboplatin and pemetrexed, low TS mRNA and protein levels were associated with improved disease control (p=0.027), improved PFS (p=0.017) and OS (p=0.022), but ERCC1 expression did not affect clinical outcome (20). These studies suggest that in patients who are treated with a pemetrexed based regimen, low TS expression is associated with improved outcome. However, these results need to be confirmed in a prospective clinical trial before they are used in routine clinical practice.

2.1.2. Gemcitabine—Gemcitabine is an anti-folate that has activity against a variety of solid and hematological malignancies. The antitumor activity of single agent gemcitabine in malignant mesothelioma is limited with a response rate of between 0% and 31% [21]. Therefore several studies have evaluated gemcitabine in combination with a platinum compound. A Phase II study evaluated combined cisplatin 100 mg/m^2 day 1 and gemcitabine 1,000 mg/m^2 days 1, 8 and 15 of a 28 day cycle for six cycles in patients with advanced measurable pleural mesothelioma [22]. There were no complete responses seen in the 21 patients who were treated. A partial response was seen in 10 (47.6%) patients (95% CI, 26.2% to 69.0%). In 9 of the 10 responding patients, the histology was that of an epithelial subtype. Median response duration was 25 weeks, progression-free survival was 25 weeks (95% CI, 17–33 weeks) and overall survival was 41 weeks (95% CI, 24–59 weeks). Four additional trials combining gemcitabine with cisplatin have led to modest response rates of between 12% and 48% and a median overall survival of 9.4–13 months [23–26].

Chemotherapeutic regimens employing a platinum agent are considered more toxic than non-platinum-based treatments. A number of studies have evaluated the substitution of a non-platinum partner to an antifolate in MPM. Single agent gemcitabine has a response rate of between 0% and 31% [21] and single agent pemetrexed has a 16% response rate [27]. Preclinical and clinical data in many solid tumor types suggested that there was a synergistic antitumor effect when gemcitabine and pemetrexed were combined [28–30]. A Phase II trial evaluating the combination of pemetrexed and gemcitabine in 108 chemotherapy-naïve patients (56 patients in cohort 1 and 52 patients in cohort 2) with MPM was performed [31]. Two different dosing schedules based on conflicting preclinical and clinical data were assessed. Cohort 1 received gemcitabine 1,250 mg/m^2 on days 1, 8 with pemetrexed 500 mg/m^2 on day 8 and cohort 2 received the same gemcitabine schedule but pemetrexed 500 mg/m^2 was administered on day 1. Cycles were repeated every 21 days. Response rates were 26.0% in cohort 1 and 17.1% in cohort 2. Median time to disease progression was 4.34 months for cohort 1 and 7.43 months for cohort 2. Median survival was 8.08 months for cohort 1 (1 year survival, 31.4%) and 10.12 for cohort 2 (1 year survival, 45.8%). The observed response rates with this combination are lower than the 41.3% reported in the Phase III study of cisplatin/pemetrexed [10] and are not much larger than the 14.5% response rate documented in the Phase II study of single agent pemetrexed [27]. Furthermore, the combination of gemcitabine and pemetrexed was associated with significant hematologic toxicity with grade 3/4 neutropenia occurring in more than 50% of patients in cohort 2. This study suggests that non-platinum based chemotherapy combinations are suboptimal in MPM and therefore platinum plus an antifolate remains the standard of care.

Prior to the phase III trial that established pemetrexed plus cisplatin as the new standard for front-line treatment of mesothelioma, the combination of gemcitabine plus cisplatin was commonly used for treating newly diagnosed patients. At present, treatment with gemcitabine plus a platinum compound is a reasonable option for second line treatment outside of a clinical trial. Since single agent gemcitabine by itself has limited activity combination treatment is probably more appropriate. Also based on the studies conducted by Janne et al. treatment with gemcitabine plus pemetrexed for front-line therapy is less effective and associated with more toxicity [30, 31].

2.1.3. Vinorelbine—Vinorelbine, a microtubule inhibitor, either alone or in combination with other agents, has been tested in mesothelioma in both frontline and relapsed settings. In a small Phase II study of 29 patients with untreated pleural mesothelioma vinorelbine, administered at 30 mg/m^2 weekly for 6 consecutive weeks per cycle, resulted in a response rate of 24% and a median overall survival of 10.6 months [32]. The combination of

vinorelbine and cisplatin as frontline therapy was assessed in 54 patients. In this study, each cycle consisted of weekly vinorelbine 25 mg/m^2 and cisplatin 100 mg/m^2 every 4 weeks. There were 2 complete responses and 14 partial responses for a response rate of 29.6% and a median survival time of 16.8 months [33]. Although the response rates of vinorelbine either alone or in combination with cisplatin are encouraging, there is no data from randomized clinical trials to justify its use for treating newly diagnosed patients with mesothelioma.

Single agent vinorelbine was assessed in the second line setting for patients with relapsed MPM who had previously received chemotherapy, excluding a vinca alkaloid. In this trial of 63 patients with pleural mesothelioma, weekly vinorelbine demonstrated a response rate of 16% and an overall survival of 9.6 months [34] (Table I). A phase II trial evaluated vinorelbine (25mg/m^2) combined with gemcitabine (1000mg/m^2) on days 1 and 8 every 3 weeks in 30 patients that had previously received pemetrexed as first line therapy [35]. This regimen had an acceptable toxicity profile and was moderately active in the second line setting with a 10% response rate and median overall survival of 10.9 months. The data from these small trials of vinorelbine in patients with relapsed mesothelioma show that it has some anti-tumor activity in patients who have failed first line therapy. It appears that single agent vinorelbine may be just as active and better tolerated than when given in combination with gemcitabine. In the absence of other treatment options, and outside the context of a clinical trial single agent vinorelbine is reasonable second line treatment for patients with pleural mesothelioma.

Vinorelbine has also been evaluated in malignant mesothelioma as a component of the MS01 trial that was performed to help answer the question as to whether the addition of chemotherapy improved survival over active symptom control (ASC) alone [36]. Over 400 patients were randomized to receive ASC alone (n=136) or ASC with mitomycin 6mg/m^2, vinblastine 6mg/m^2, and cisplatin 50mg/m^2 (MVP) every 3 weeks (n=137) or to ASC plus vinorelbine 30mg/m^2 every week for 12 weeks (n=136). Due to slow accrual, the two chemotherapy arms were combined and compared to ASC alone to assess the primary outcome of OS. The addition of chemotherapy to ASC did not result in an improvement in overall survival although post-hoc exploratory analysis suggested that addition of vinorelbine to ASC may improve overall survival. However, the findings of this study are limited by the fact that the original study design, which would have required a total of 840 patients to detect a 3 month improvement in overall survival in the ASC plus MVP or ASC plus vinorelbine arm, was not accomplished because of slow accrual. Also the improvement in survival in the ASC plus vinorelbine arm as compared to ASC alone reported in this trial was based on an exploratory analysis and was not statistically significant. The median overall survival in all the three arms of the MS01 trial was similar to that seen in the control arms i.e. cisplatin alone, of the randomized phase III trials of pemetrexed and raltitrexed and inferior to the benefit seen in patients who received cisplatin with either pemetrexed or raltitrexed.

2.2. TARGETED THERAPY

2.2.1. Epidermal growth factor receptor inhibitors—The proliferation and spread of malignant mesothelioma cells has been shown to be related to a number of growth factors and their receptors, including epidermal growth factor receptor (EGFR), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) [37–38]. As a result, a number of clinical trials have enlisted targeted agents to these receptors in an attempt to inhibit mesothelial cell growth. To date efficacy data for novel agents in mesothelioma has been disappointing.

EGFR inhibitors were thought to be a promising target for mesothelioma therapy since studies showed that EGFR was highly expressed in malignant mesothelioma [38–39].

However, the results of these agents have been disappointing. In a phase II clinical trial of gefitinib in 43 patients with previously treated mesothelioma only one partial and one complete response were observed, despite the fact that 97% of the tumors had EGFR over-expression [40]. Similarly, a second Phase II study confirmed the limited activity of gefitinib with only 1 partial response out of 20 evaluable patients [41]. A phase II clinical trial of erlotinib also showed lack of activity in mesothelioma [42]. In addition, the combination of erlotinib plus bevacizumab in previously treated MPM patients had no anti-tumor activity[43]. The results of these clinical trials demonstrate that EGFR inhibitors have no efficacy in pleural mesothelioma, which is most likely due to absence of sensitizing mutations in the EGFR tyrosine kinase domain[44].

2.2.2. Angiogenesis inhibitors—Since patients with mesothelioma have very high VEGF levels there has been active interest in VEGF inhibition in this disease setting, particularly with the monoclonal antibody bevacizumab [45]. Ongoing clinical trials are investigating various combinations of bevacizumab with approved and investigational agents. To date no study involving an anti-angiogenic agent has shown proven efficacy in improving response or overall survival in malignant mesothelioma. A randomized Phase II trial combining cisplatin and gemcitabine with and without bevacizumab in chemotherapy-naïve patients showed no overall benefit to the regimen, despite promising preclinical data [45]. The primary endpoint of progression free survival did not reach statistical significance with 6.9 months versus 6.0 months (HR 0.93, P=0.88) in the bevacizumab and placebo arms, respectively.

The multicenter randomized phase II/III IFCT-GFPC-0701 MAPS trial is investigating pemetrexed-cisplatin with or without bevacizumab[46]. Unresectable chemotherapy naïve patients receive pemetrexed 500 mg/m2, CDDP 75 mg/m2 (PC) at D1, with (arm B) or without bevacizumab (arm A), 15 mg/kg Q21D, for 6 cycles. Patients randomized to arm B receive bevacizumab maintenance therapy until progression or toxicity. The primary endpoint of this trial is to assess the percentage of non-progressive patients at 6 months. In a preliminary report there were no significant differences in grade 3/4 toxicity between the two arms. The final results of this trial are eagerly awaited to see if addition of bevacizumab to the backbone of pemetrexed and cisplatin can improve the outcome for these patients.

Phase II studies investigating single agent small molecule VEGF tyrosine kinase inhibitors have shown only modest activity. Sorafenib was evaluated in a single arm Phase II study in chemotherapy-naïve and previously treated patients with MPM. Only modest activity was seen with only 3 (6%) out of 50 evaluable patients obtaining a partial response [47]. Patients who had received prior chemotherapy had a median OS of 13.2 months Vs 5.0 months for patients who were treatment naïve (p=0.3117). One-year survival was also greater in previously treated patients (57% vs 30%). Patient selection issues rather than true clinical activity in this patient population have been suggested as the reason for patients in the second line setting doing better. Similarly, Vatalanib, which inhibits both the VEGF receptor and the PDGF receptor, had limited activity in a phase II study with an 11% response rate and a median survival time of 10 months in untreated patients [48–49]. Another angiogenesis inhibitor, Sunitinib has modest activity in this disease with a response rate of 10%, median TTP of 3.4 months and a median OS of 6.7 months as a single agent in the second line setting. Metabolic responses as measured by FDG-PET in patients without prior talc pleurodesis were seen in 7 out of 20 (35%) assessable patients, one of whom had a PR on CT and four had minor CT responses[50]. In summary, phase II clinical trials of VEGF tyrosine kinase inhibitors have shown at best modest activity in mesothelioma and are not recommended for routine clinical use.

Thalidomide is the oldest and perhaps the most extensively studied drug of all the available anti-angiogenic agents. In a small phase II study of patients with untreated or previously treated mesothelioma, 11 (27.5%) out of 40 evaluable patients showed disease stabilization of > 6 months [51]. The utility of thalidomide in MPM is being evaluated in the randomized Phase III study NVALT 5/ MATES (Maintenance Thalidomide in Mesothelioma Patients). This study, which has completed accrual, is investigating the role of maintenance thalidomide in those patients showing disease stabilization or response after first line pemetrexed chemotherapy with or without a platinum. The results of this phase III study are eagerly awaited to determine if maintenance treatment with an anti-angiogenic agent is beneficial in patients with mesothelioma.

2.2.3. Proteasome-modifying treatments—Preclinical studies show that bortezomib induced inhibition of NF-κ-β enhances the activity of cisplatin and pemetrexed therapy [52–53]. On the basis of this preclinical data, there are three ongoing clinical trials investigating proteasome inhibitors in patients with MPM. The first is a single agent phase II trial whereby 111 patients will be enrolled with 57 patients treated in the first line setting and 54 patients in the second line setting. Patients receive bortezomib on days 1, 8, 15, and 22. Treatment repeats every 5 weeks for up to 4 courses in the absence of disease progression or unacceptable toxicity. Patients exhibiting objective response or stable disease by week 20 may continue treatment at the discretion of the investigator until evidence of disease progression. The second phase II trial is investigatingthe combination of bortezomib (on days 1, 4, 8, and 11) and cisplatin (on day 1) as a first line regimen. Treatment repeats every 3 weeks for up to 6 courses in the absence of disease progression or unacceptable toxicity. Another phase II trial is investigating the combination of bortezomib and oxaliplatin in previously treated patients. A cycle is comprised of four treatments of bortezomib 1.3 mg/m^2 given on days 1, 14, 15, and 18 and two treatments of oxaliplatin 85 mg/m^2 on days 4 and 18, every 28 days. The single agent bortezomib trial and bortezomib plus oxaliplatin trial are open to patient accrual, while the bortezomib plus cisplatin trial now closed.

2.2.4. Histone deacetylase inhibitors—The post-translational modification of proteins plays an important role in controlling gene transcription. Histone deacetylases (HDACs) are regulatory enzymes that manipulate chromatin structure and function. The most studied post-translational modification of histones is the acetylation of lysine. HDACs are further involved in reversible acetylation of a number of non-histone proteins, such a p53, tubulin, as well as various transcription factors and other proteins [54–56]. Preclinical data suggests that HDACs play a critical role in the malignant transformation and cellular differentiation in mesothelioma [57]. It is also thought that the HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) represses the gene for thymidylate synthase, which is the target of pemetrexed.

In a Phase I study of SAHA (Vorinostat) in patients with advanced cancer, two of the thirteen mesothelioma patients treated had a partial response [58]. A Phase III trial is currently ongoing, in which 660 patients with previously treated mesothelioma are being randomized to either vorinostat or to placebo with overall survival as its primary endpoint (Table II). Patients cannot have received more than 2 prior chemotherapy regimens. Vorinostat is administered at a dosage of 300mg twice daily for 3 consecutive days followed by 4 days of rest repeated weekly, in 21-day treatment cycles. Treatment continues until disease progression or unacceptable toxicity. The results of this study are eagerly awaited as it represents one of the largest trials ever performed in MPM. If the results of this study are positive it could represent another treatment option for patients who have progressed on a pemetrexed based regimen.

2.2.5 Other targeted agents—The Src family of tyrosine kinases and its ligands are commonly over-expressed in MPM. Dasatinib is a potent inhibitor of SRC family kinases,

EphA2 and PDGFRβ. The CALGB conducted a phase II study of dasatinib in patients with previously treated unresectable MPM. Unfortunately the drug was poorly tolerated and had no activity[59]. Similarly, Imatinib, a tyrosine kinase inhibitor of PDGF and c-Kit, as a single agent failed to demonstrate activity in MPM[60–61]. However, ongoing combination studies with gemcitabine and with cisplatin/pemetrexed will determine if it has a role in this disease[62–63].

A phase II trial of the mTOR inhibitor, Everolimus, is currently ongoing with the primary endpoint to determine the 4-month PFS in patients previously treated with a platinum based regimen. In this trial patients receive oral everolimus once daily on days 1–28 with repeat courses every 28 days.

Another interesting ongoing phase II study in patients with previously treated MPM is investigating the human IgG4 kappa monoclonal antibody (GC1008) capable of neutralizing all mammalian forms of TGFβ (β1, β2, β3). Approximately 20 patients are expected to enroll with the primary endpoint being PFS at 3 months.

Cell cycle G_2 checkpoint abrogation is an attractive strategy for sensitizing cancer cells to DNA-damaging anticancer agents without increasing adverse effects on normal cells. The peptide CBP501, has focused activity against MAPKAP-K2, C-Tak1, and CHK1[64]. An ongoing phase I/II study is evaluating the combination of CBP501 with full dose cisplatin and pemetrexed. Upon determination of the MTD, the phase II part will evaluate the 3 drug combination in previously untreated, unresectable MPM. Patients will be randomized in a 2:1 ratio to pemetrexed, cisplatin and CBP501 (Arm A) or to pemetrexed and cisplatin (Arm B) alone.

2.3. IMMUNOTHERAPY

2.3.1. Anti-mesothelin antibodies—Mesothelin is a tumor differentiation antigen that is present on mesothelial cells lining the pleura, peritoneum and pericardium. It is also highly expressed in several human cancers including malignant mesothelioma, as well as pancreatic, ovarian and lung adenocarcinomas [65–68]. Mesothelin expression occurs in 100% of epithelial mesotheliomas but is absent in sarcomatoid subtypes [65, 69].

The normal biological function of mesothelin is unknown. Recent data suggest mesothelin binds to MUC16/CA-125 and may play a role in the peritoneal spread of ovarian cancer [70]. It is proposed that mesothelin is a novel CA-125 binding protein that allows intraperitoneal dissemination via enhanced adhesion to normal mesothelial cells lining the peritoneal cavity. Mesothelin expression has also been shown to be regulated by the Wnt signaling pathway which plays an important role in cell growth, cell differentiation and apoptosis [71]. The limited expression of mesothelin on normal human tissues and high expression in epithelial mesotheliomas makes it an attractive cancer target. Therapies have been developed that target cell surface mesothelin or elicit an immune response against mesothelin.

SS1P – is a high affinity (KD = 0.72 nM) anti-mesothelin disulfide-stabilized murine-antibody Fv genetically combined with PE38 [72]. PE38 is a fragment of the potent cytotoxic *Pseudomonas* exotoxin lacking the native cell-binding domain. It is this truncated *Pseudomonas* exotoxin linked to the anti-mesothelin Fv that mediates cell killing. In preclinical studies, SS1P is cytotoxic to mesothelin expressing cell lines and causes regression of mesothelin expressing tumor xenografts in nude mice. Two phase I clinical trials of SS1P using different schedules of administration have been completed. In one clinical trial, escalating doses of SS1P were administered as a bolus infusion every other day in patients with advanced mesothelin-expressing malignancies who had failed prior

treatments (62). The maximum tolerated dose of SS1P was 45 μg/kg every other day × 3 doses, and the dose limiting toxicity was pleuritis seen in two of two patients treated at 60 μg/kg dose level. In this group of heavily pre-treated patients there was some evidence of anti-tumor activity including minor responses and resolution of ascities (62). The second clinical trial of SS1P administered as continuous infusion showed a similar toxicity profile and the maximum tolerated dose was 25μg/kg/day × 10 day infusion (63). Since SS1P given as bolus infusion has a prolonged half-life, approximately 8 hours, and the continuous infusion showed no significant benefit over bolus dosing, the bolus infusion schedule has been adopted for future clinical trials. A Phase I trial is ongoing in patients with advanced unresectable mesothelioma whereby subjects receive pemetrexed and cisplatin in addition to a bolus dosage of SS1P. Patients enrolled receive six cycles of standard care chemotherapy of pemetrexed and cisplatin. However, for the first two cycles, patients receive doses of SS1P on days 1, 3, and 5 at escalating dose cohorts of 25 mcg/kg, 35 mcg/kg, 45 mcg/kg, and 55 mcg/kg. The trial is now in the expansion phase.

MORAb-009 is a high affinity chimeric (mouse/human) monoclonal IgG/κ antibody consisting of the heavy and light chain variable regions of a mouse anti-mesothelin single chain Fv grafted in frame to human IgG1 and κ constant regions. MORAb-009 kills mesothelin expressing cell lines via antibody dependent cellular cytotoxicity and it inhibits the binding of mesothelin to CA-125 [73]. MORAb-009 is currently being evaluated in a phase II clinical trial of patients with unresectable MPM. In this trial, MORAb-009 is administered concurrently with pemetrexed and cisplatin. The patients undergo a standard set of 6 cycles of pemetrexed and cisplatin, with MORAb-009 given on days 1 and 8 of each 3 week cycle of combination chemotherapy. After the 6 cycles of combination treatment, patients continue receiving MORAb-009 as maintenance therapy until disease progression. A preliminary analysis from this trial is not yet available, and enrollment remains active.

2.3.2 Anti-mesothelin vaccines—The rationale for mesothelin as a tumor vaccine is based on studies showing that mesothelin can elicit a strong CD8+ T cell response in patients[74]. CRS-207 is vaccine that utilizes as a vector a live-attenuated strain of the bacterium *Listeria monocytogenes* encoding human mesothelin [74]. Preclinical studies show that CRS-207 elicits human mesothelin-specific CD4+/CD8+ immunity in mice and in cynomolgus monkeys and exhibits therapeutic efficacy in tumor bearing mice. A Phase I clinical trial of CRS-207 for the treatment of patients with mesothelin expressing cancers was recently reported[75]. In this phase I study 17 patients with mesothelin expressing cancers including 5 with mesothelioma were treated at different dose levels and the maximum tolerated dose was 1×10^9 cfu. Although no tumor shrinkage was noted in this group of heavily pre-treated patients a mesothelin-specific T cell response was observed in 5 out of 10 patients tested. Based on the tolerability and immune activation, CRS-207 may be an attractive agent to treat mesothelioma either alone or in combination with other agents.

2.3.3 Gene therapy—Albelda *et al*. have pioneered adenovirus based gene therapy in MPM. Early work evaluated adenovirus vectors containing the herpes virus thymidine kinase (Ad-HSVtk) suicide gene administered intrapleurally followed by intravenous ganciclovir [76–77]. It was envisioned that initially the viral thymidine kinase would be introduced into the cancer cells and then when ganciclovir was administered it would be metabolized to the cytotoxic ganciclovir triphosphate leading to apoptosis. A Phase I study of 21 patients with treatment-naïve MPM evaluated intrapleural Ad-HSVtk followed by 2 weeks of ganciclovir [78]. The trial demonstrated proof of principle with 11/20 patients having transfer of the HSVtk gene into their tumors and 2 patients had a long term survival over 6.5 years [79]. Immune modulation rather than a direct antitumor effect was felt to be the underlying reason for efficacy. Intrapleural administration of adenoviral vector expressing interferon beta (Ad.IFN-β) was subsequently evaluated in a Phase I trial of 10

patients. The trial demonstrated gene transfer, humoral antitumor immune responses, and disease stability in 3 of 10 patients at 2 months after a single dose of Ad.IFN-β [80]. A follow up Phase I trial was conducted to determine whether using two doses of Ad.IFN-β vector would be superior [81]. No increased efficacy was observed and the authors concluded that rapid development of neutralizing antibodies prevented effective gene transfer after the second dose, even with a dose interval as short as 7 days. Ongoing studies are continuing to evaluate the strategy of gene therapy in MPM.

3. Conclusion

Modest improvements in the treatment of unresectable malignant mesothelioma with chemotherapy have been made in the last decade. The combination of cisplatin and pemetrexed remains the standard of care chemotherapeutic regimen. Results of ongoing trials investigating bevacizumab with cisplatin and pemetrexed for newly diagnosed patients, and of pemetrexed and thalidomide as maintenance therapies, as well as vorinostat and retreatment with pemetrexed in the second line setting, are eagerly awaited and could further improve the prognosis of these patients. Multiple targeted therapies such as EGFR and VEGF inhibitors have been studied in mesothelioma but so far, have had limited activity. The personalization of chemotherapy from the limited menu of cytotoxics that are active in mesothelioma is one strategy that may lead to improved clinical outcomes. Ongoing trials are investigating thymidylate synthase and excision repair cross-complementing group 1 as possible predictive markers for pemetrexed and platinum agents respectively. Immunotherapeutics using novel agents such as SS1P and MORAB 009 and future clinical trials of targeted agents as directed by molecular profiling based analysis of an individual patient's tumor may result in further advances in mesothelioma therapy.

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TABLE I

Selected phase II and phase III combination chemotherapy trials in un-resectable MPM

Chemotherapy	Phase II/III (n)	RR	Median PFS (mnths)	Median OS (mnths)	Reference
Cisplatin + Pemetrexed Vs Cisplatin	III (456)	41.3% Vs 16.7%	5.7 Vs 3.9	12.1 Vs 9.3	[10]
Cisplatin + Pemetrexed Or Carboplatin + Pemetrexed	EAP (1704) EAP	26.3% 21.7%	7.0 6.9	63.1% (1 yr OS) 64% (1 yr OS)	[16] [16]
Cisplatin + Raltitrexed Vs Cisplatin	III (250)	23.6% Vs 13.6%	5.3 Vs 4.0	11.4 Vs 8.8	[11]
Pemetrexed + Gemcitabine	II (108)	17–26%	7.4	10.1	[31]
Cisplatin + Gemcitabine	II (50)	12%	6.0	10.0	[24]
Cisplatin + Vinorelbine	II (54)	29.6%	7.2	16.8	[33]
Chemotherapy (MVP or V) Vs ASC alone	III (409)	12%	5.6 Vs 5.1	8.5 Vs 7.6	[36]

RR, response rate; PFS, progression free survival; OS, overall survival; EAP, international expanded access program; MVP, mitomycin, vinblastine, and cisplatin; ASC, active symptom control; V, vinorebline

TABLE II

Targeted agents in malignant pleural mesotheliomas

Novel agent	Phase (n)	RR	Median PFS (mnths)	Median OS (mnths)	Reference
Gefitinib	II (43)	4%	2.6	6.8	[40]
Erlotinib	II (63)	0%	2.0	10.0	[42]
Bevacizumab + Cisplatin/Gemcitabine Vs Cisplatin/Gemcitabine	II (115)	25% Vs 22%	6.9 Vs 6.0	15.6 Vs 14.7	[45]
Sorafenib	II (51)	4%	3.7	10.7	[47]
Vatalanib	II (47)	11%	4.1	10.0	[49]
Sunitinib	II (23)	15%	3.5	5.9	[50]
Thalidomide	II (40)	27.5% SD	NR	7.6	[51]
Vorinostat	I (13)	15%	NR	NR	[58]

PFS, progression free survival; OS, overall survival; PR, partial response; SD, stable disease; NR, not reported