Review Article

Target therapy: new drugs or new combinations of drugs in malignant pleural mesothelioma

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Abstract: Malignant pleural mesothelioma (MPM) is a disease with a poor prognosis due to its aggressive nature. The management of patients with MPM is controversial. Considering that the contribution of surgery and radiation therapy in the management of this disease is not yet established, systemic treatments are predominantly considered during the course of MPM. Unfortunately, the currently therapeutic armamentarium is scarce and its outcomes still appear modest. New treatment strategies are needed. In preclinical setting, cell cycle regulation, apoptosis, growth factor pathways, and angiogenesis pathways involved in the development of MPM have been identified. However, in clinical setting, several drugs targeting these pathways resulted without a significant activity. A deeper knowledge of the biology and pathogenesis of this disease is required to develop more effective tools for diagnosis, therapy and prevention. This paper reviews therapeutic advances in MPM, with a particular focus on new drugs and new association of drugs of target therapy.

Keywords: Malignant pleural mesothelioma (MPM); target therapy; new drugs; new association of drugs

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Introduction

Malignant pleural mesothelioma (MPM) is a neoplasm with a poor prognosis. Despite the use of asbestos has been banned in several countries of the world, the incidence of this disease is globally increasing (1).

The management of patients affected by MPM is not established, yet. Few patients are candidates for multimodality treatment whereas the contribution of surgery and radiation therapy in the management of MPM is not yet defined. Therefore, patients are predominantly treated with systemic treatments during the course of this disease (2). The antifolates pemetrexed and raltitrexed were shown to be active in MPM if combined with platinum compounds. A large phase III trial comparing cisplatin pus pemetrexed *vs.* cisplatin alone in 448 chemo-naïve MPM patients demonstrated that the combined regimen was statistically significantly better in terms of overall survival (OS), time to progression (TTP), response rate (RR), symptom control and quality of life (3). The raltitrexed/cisplatin combination achieved similar results, with a weaker statistical significance (4). Therefore, cisplatin/pemetrexed combination is considered today the standard of care in first line setting for MPM patients. Pemetrexed alone or combined with carboplatin represents a valid alternative in case of patients unfit to receive a cisplatin-based chemotherapy, because able to reduce toxicity maintaining similar survival outcomes (5-8). Unfortunately, the majority of MPM patients' progress during or after first-line chemotherapy and the role of second-line chemotherapy in MPM are not yet defined (9). Moreover, considering the long latency between asbestos exposure and diagnosis, there is a high proportion of elderly patients with MPM, often with a poor performance status due to associated comorbidities (10,11). In clinical practice, vinorelbine still remains an acceptable therapeutic strategy in second line setting. Re-treatment with a pemetrexed-based regimen should be considered only in selected cases (12,13). Overall,

Table 1 New drugs or new combinations of drugs in malignant pleural mesothelioma

Target	Drugs	Combinations	Trial design	Setting	http://clinicaltrials.gov/
VEGF/VEGFR	Bevacizumab	CDDP-PEM	Phase II/III	First line	NCT00651456
	Nintedanib	CDDP-PEM	Phase II/III	First line	NCT01907100*
	Ramucirumab	Alone	Phase II	Second line	GOIRC-03-2016*§
	Imatinib	GEM	Phase II	Second line	NCT02303899**
	NGRhTNF	Alone	Phase II	Maintenance	NCT01358084*
	NGRhTNF	GEM/VNR/DOX	Phase III	Second line	NCT01098266**
Mesothelin	SS1P	CDDP-PEM	Phase I	First line	NCT01445392
	SS1P	Pentostatin/Cyclop	Phase I/II	Second line	NCT01362790**
	Amatuximab	CDDP-PEM	Phase II	First line	NCT02357147**
	Anetumab/Rav	Alone	Phase II	Second line	NCT02610140**
	Anetumab/Rav	CDDP-PEM	Phase Ib	First line	NCT02639091*
	CRS2017	CDDP-PEM	Phase Ib	First line	NCT01675765**
Met	Tivantinib	CBDCA-PEM	Phase I/Ib	First line	NCT02049060**
FAK	Defactinib	Alone	Phase II	Neo-adjuvant	NCT02004028

*, recruiting; **, not recruiting; §, not registered on www.clinicaltrials.gov. GOIRC, number identifier.

the currently available therapeutic armamentarium for MPM is poor and new treatment strategies are urgently required.

In recent years, several molecular modifications and new targets were identified in MPM (14,15). The main pathways explored include growth factors and angiogenesis (i.e., EGFR, PDGFR, VEGF and VEGFR pathway), cell-cycle regulators and apoptosis (i.e., NF-kB pathway), epigenetic modulators (acetylation/deacetylation of DNA). Unfortunately, several agents targeting these processes have proven ineffective in clinical trials.

The purpose of this manuscript is to critically review the literature data regarding new drugs and new association of drugs for the treatment of MPM patients with a particular focus on target therapy, overviewing ongoing trials and future perspectives.

Anti-angiogenic drugs

The role of angiogenesis in the biology of MPM is well established. A high expression of VEGF and its receptors (VEGFR-1, VEGFR-2 and VEGFR-3) was found in MPM cell lines, tissue, and pleural effusions (16-18). Compared to normal mesothelial cells, VEGF and its receptors (VEGFR-1 and VEGFR-2) resulted highly expressed in MPM cell lines, leading to an increased cell proliferation (18). Furthermore, the serum concentrations of VEGF resulted significantly higher in MPM patients than in normal subjects (19). On the basis of these preclinical data, several anti-angiogenic drugs have been evaluated or are still under study in clinical setting, both as first-line therapy and in pretreated MPM patients. Unfortunately, phase II trials of vatalanib (PTK787), semaxinib (SU5416), thalidomide, dasatinib, sunitinib, and sorafenib, and phase III trial of thalidomide as maintenance therapy after first line chemotherapy, have demonstrated only modest activity in MPM patients (20-28).

Bevacizumab

Bevacizumab is the most studied molecule (*Table 1*). The combination of cisplatin with gemcitabine plus bevacizumab or placebo in MPM patients in the first line setting was evaluated in a randomized, phase II trial (29). Primary endpoint of the study was progression-free survival (PFS). Adding bevacizumab to chemotherapy with cisplatin and

gemcitabine did not yield statistically significant differences in terms of PFS (6.9 *vs.* 6.0 months; HR 0.93; P=0.88), in terms of OS (15.6 *vs.* 14.7 months; HR 1.13; P=0.91), in terms of 1-year survival (59% *vs.* 57%), and in terms of response (RR: 25% *vs.* 22%; stable disease: 51% *vs.* 60%). Patients with high baseline plasma-VEGF levels showed poorer prognosis. A synergism between pemetrexed and bevacizumab was demonstrated in mice with orthotopically implanted human mesothelioma cells (30). Several trials of bevacizumab combined with chemotherapy (platinum compound plus pemetrexed) in the first-line treatment of unresectable MPM have been reported. Two of these studies are single arm phase II trials and their results appear similar and seem to compare favorably with historical controls of major trials with cisplatin or carboplatin with antifolates (31,32). RR and disease control rate (DCR) observed in these trials were around 40% and 80%, respectively, whereas median PFS and OS were in the range of 6.9–7.9 and 14.3–14.8 months. A phase II/III trial of 448 chemotherapy-naive patients with unresectable MPM treated with the combination of pemetrexed and cisplatin or pemetrexed and cisplatin plus bevacizumab for six cycles was conducted (33). The primary endpoint of this study was OS. The combination of bevacizumab plus cisplatin and pemetrexed significantly improved OS with an increase of 2.7 months (18.8 *vs.* 16.1 months; HR 0.77; P=0.0167). However, as acknowledged by the authors themselves, the study population was likely selected by positive prognostic factors, as confirmed by the surprisingly high median OS (16.1 months) in the control arm. Elderly patients, which represent a significant percentage of MPM cases observed in every day practice, were substantially excluded. In fact, median age of patients enrolled in the MAPS trial was 65.7 years (range, 18–75 years), while median age at diagnosis in Europe and U.S. is nearly 70 years, with at least a quarter of cases over 75 years. Moreover, MPM patients are often affected by co-morbidities, a recognized negative prognostic factor. In the MAPS trial, the strict selection criteria for bevacizumab and cisplatin, including a creatinine clearance of ≥60 mL/min, have led to a further patient selection. In spite of that very favorable patient selection, the incidence of severe toxicity was relevant with an overall grade 3–4 adverse events rate of 71% in the bevacizumab arm *vs.* 62% in the chemotherapy alone arm, leading to a treatment interruption in 24.3% of cases in the bevacizumab arm *vs.* 6% in the chemotherapy alone arm. Of note, in the bevacizumab-containing regimen, grade 3–4 cardiovascular AEs were increased by 27.9%, despite exclusion at the study entry of patients with cardiovascular co-morbidities. Although these toxicities may limit patient eligibility in the everyday practice, MAPS trial is the first study that demonstrates a survival advantage of an anti-angiogenic agent combined with chemotherapy in the treatment of MPM patients.

Nintedanib

Nintedanib is a triple kinase inhibitor of VEGFR (VEGFR-1 and VEGFR-3), PDGFR (PDGFR alpha/beta), and FGFR (FGFR-1 and FGFR-3), as well as Src and Abl kinases, which are involved in regulating tumor angiogenesis, growth, and metastasis of MPM. LUME-Meso is an international, double-blind, placebo-controlled, randomized phase II/III study designed to evaluate efficacy and safety of nintedanib combined with pemetrexed/cisplatin for the treatment of unresectable MPM. Chemo-naïve patients with ECOG performance status 0–1 and with epithelioid/biphasic MPM histology are randomized (1:1) to receive the combination of pemetrexed/cisplatin plus nintedanib or placebo. Patients without disease progression continue to receive maintenance treatment with nintedanib monotherapy/placebo. Progression free survival is the primary endpoint, whereas OS is the key secondary endpoint. The data of phase II study were recently presented (34). Eighty-seven patients were randomized. The PFS was longer in the nintedanib *vs.* the placebo arm, in both the overall study population (9.4 *vs.* 5.7 months; HR 0.56; P=0.017) and in the epithelioid patients (9.7 *vs.* 5.7 months; HR 0.51; P=0.010). Preliminary OS data also favor nintedanib. In the nintedanib arm, 7% of patients discontinued due to adverse events compared to 15% with placebo. The most frequent grade 3–4 adverse events observed in the nintedanib arm *vs.* placebo arm were neutropenia (34% *vs.* 10%), ALT increase (14% *vs.* 2%), and gamma-glutamyl transferase increase (14% *vs.* 0%). Based on these findings, this phase II study was extended to a confirmatory phase III trial, which is currently enrolling patients (ClinicalTrials.gov identifier NCT01907100).

Ramucirumab

Ramucirumab (IMC-1121B, LY3009806) is a monoclonal antibody built to selectively bind the extracellular domain of human VEGFR-2 with a higher affinity than its natural ligands. Targeting VEGFR-2 on MPM cells, ramucirumab

directly inhibits tumor proliferation. Moreover, due to VEGF-R2 expression on macrophages, ramucirumab is also able to inhibit macrophages leading to a decrease of tumor immune infiltration, cytokine and chemokine release, which thereby decrease tumor growth and proliferation (35). A randomized, placebo-controlled phase II trial (RAMES Study) comparing gemcitabine with or without ramucirumab in second line setting in MPM patient is recruiting (GOIRC identifier GOIRC-03-2016). The primary endpoint of this study is OS. Secondary efficacy objectives for this study include comparison of PFS, ORR and DCR.

Imatinib

Imatinib is a tyrosine kinase inhibitor of PDGFRb, c-kit, bcr-abl, and c-fms. As monotherapy, it largely failed to show significant activity in MPM (36). *In vitro* studies showed that imatinib synergizes with chemotherapeutic agents in PDGFRbeta-positive MPM cells, such as gemcitabine and pemetrexed (37). In an *in vivo* model, gemcitabine inhibited tumour growth, whereas pemetrexed was ineffective, even at the highest dosage tested. The combination of gemcitabine with imatinib, compared with gemcitabine alone, led to a further tumor growth inhibition and improved mice survival by a decrease rate of tumour cell proliferation and an increase in number of apoptotic tumour cells. *In vivo* experiments in a mouse human malignant mesothelioma xenograft model showed increased efficacy of gemcitabine when co-administered with imatinib, postulated to be due to increased gemcitabine delivery (38).

Considering the synergistic benefit observed in preclinical model with the combination of chemotherapy with imatinib, 17 chemo-naive MPM patients were treated with imatinib combined with cisplatin and pemetrexed in a phase I trial. Although some clinical benefit was observed, particularly in patients with higher baseline tumor pPDGFRa expression, epithelial histology, good performance status, and in patients able to receive all six cycles of chemotherapy, this regimen resulted toxic (39). Imatinib combined with gemcitabine is under evaluation in a phase II study enrolling pemetrexed-pretreated patients with MPM expressing PDGFRb and/or c-Kit by immunohistochemistry (ClinicalTrials.gov identifier NCT02303899). The primary endpoint of this trial is to point out the anti-tumor activity of the combination in terms of 3-month PFS rate. The secondary endpoints included OS, RR and safety.

Asparagine-glycine-human tumor necrosis factor alpha (NGR-hTNF)

NGR-hTNF is an anti-angiogenic drug. The tumor necrosis factor alpha (TNFα) has a potent antivascular activity caused by a tumor-related endothelial cells apoptosis. This mechanism leads to an increase of the chemotherapeutic drugs uptake into the tumor cells. To avoid the toxicity of systemic administration of TNFα, a recombinant fusion protein of NGR-peptide and human TNFα binding CD-13 overexpressed on MPM tumor blood vessels was built (40).

In preclinical setting, NGR-hTNF demonstrated anti-tumor activity both at low and at high doses (41). In clinical setting, low-doses of NGR-hTNF (0.8 μg/m^2 infused every 3 weeks), given as second line chemotherapy, showed to be active in terms of PFS (2.8 months), OS (12.1 months), and DCR (46% of patients, maintained for a median of 4.7 months) with a good toxicity profile, in a phase II trial (42). Starting from these results, a phase III trial evaluating NGR-hTNF plus best investigator's choice chemotherapy *vs.* placebo plus best investigator's choice chemotherapy was activated (ClinicalTrials.gov identifier NCT01098266). The primary endpoint was OS. Preliminary results showed that the primary endpoint was not met (median OS: 8.4 *vs.* 7.9 months; HR 0.94; P=0.60) (43). However, patients with a short treatment-free interval showed a statistically significantly longer OS (median OS: 9.0 *vs.* 6.3 months; HR 0.69; P=0.02).

A randomized, double-blind, placebo-controlled, phase II trial comparing NGR-hTNF *vs.* placebo as maintenance treatment in MPM patients responder to first line pemetrexed-based chemotherapy is ongoing (ClinicalTrials.gov identifier NCT01358084). Progression free survival is the primary endpoint of this trial.

Anti-mesothelin drugs

Mesothelin is an antigen detectable in a very high percentage of MPM cells. In preclinical setting, its expression induced matrix metalloproteinase secretion and cell invasion and it was validated as a potential target with both tumor vaccines and antibody-based approaches (44). Therefore, a lot of immunotherapic strategies such as antibody-based therapeutic drugs, vaccines, and T-cell therapies targeting mesothelin are under evaluation in clinical setting.

SS1P

SS1P is an antimesothelin-immunotoxin evaluated in MPM. As monotherapy, SS1P was evaluated in phase I trials establishing the safety of mesothelin as a therapeutic target (45,46). However, antitumor activity was limited due to the developing of neutralizing antibodies against the toxin portion of SS1P.

Considering the remarkable synergism between chemotherapy and SS1P *in vivo*, SS1P was evaluated in first line setting combined with chemotherapy (cisplatin plus pemetrexed) (47). The combination resulted safe and active (RR 60% in 20 evaluable patients; 77% in 13 patients treated at the MTD of 45 mcg/kg). Serum mesothelin and serum megakaryocyte potentiating factor levels correlated with radiologic tumor response. Unfortunately, the combination with chemotherapy did not prevent the formation of the neutralizing antibodies against SS1P. In a preclinical study, the co-administration of cyclophosphamide and pentostatin in immunocompetent mice ended the formation anti-SS1P antibodies (48). Starting from these data, a pilot study was designed and pentostatin plus cyclophosphamide were administered to MPM patients before to receive SS1P. Thanks to this approach, the neutralizing antibody formation was reduced from 88% to 20% of patients (49). Major cancer regression was observed in 30% of patients and none of the patients developed opportunistic infections. To prevent the administration of a therapeutic immunosuppression, LMB-100 (RG7787), a less immunogenic antimesothelin-immunotoxin, is under evaluation in a clinical trial of pretreated MPM patients (ClinicalTrials.gov identifier NCT02798536).

Amatuximab

Amatuximab (MORAb-009) is an antimesothelin chimeric monoclonal antibody (50). In preclinical setting, amatuximab regulates the inhibition of mesothelin-dependent cell adhesion and antibody-dependent cellular cytotoxicity demonstrating an interesting antitumor activity as monotherapy in tumors expressing mesothelin. However, combined with chemotherapy resulted remarkably more active. In a phase I trial, its safety as monotherapy was established and the drug limiting toxicities observed were serum sickness and transaminitis (51).

Based on these results, amatuximab was evaluated in combination with chemotherapy (cisplatin plus pemetrexed) in a phase II trial of 89 chemonaïve MPM patients (52). Progression free survival was the primary endpoint of this study. The treatment resulted safe and well tolerated. The overall RR observed was 40% with an overall DCR of 91%. The study did not meet its primary endpoint showing a not significant improvement in PFS (6.1 months). However, the OS observed (14.8 months) resulted longer than historical data with the combination of cisplatin plus pemetrexed alone. Moreover, higher serum concentration predicted longer PFS and OS (583 days for patients with concentrations >38.2 mg/mL *vs.* 375 days) (53). Pharmacodynamic modeling showed that the infusion of amatuximab at a dosage of 5 mg/kg once per week induces a serum concentration of amatuximab >38.2 mg/mL in 80% of patients. A randomized phase II trial evaluating amatuximab 5 mg/kg combined with chemotherapy (cisplatin plus pemetrexed) in first line setting in unresectable MPM patients is ongoing (ClinicalTrials.gov identifier NCT02357147). The primary endpoint of this study is OS.

Anetumab ravtansine

Anetumab ravtansine (BAY94-9343) is an antimesothelin antibody. In preclinical model, it demonstrated to be particularly active in killing selectively tumor cell expressing mesothelin (54).

In clinical setting, anetumab ravtansine was firstly evaluated as monotherapy in a phase I trial of patients with cancer expressing mesothelin (included MPM patients) (55). In first line setting, objective tumor response and stable disease were observed in 5 (31%) and 7 (44%) out of 16 MPM patients, respectively. On the other hand, in second line setting, objective response and stable disease were observed in 5 (50%) and 4 (40%) out of 10 patients, respectively.

On the basis of these results, anetumab ravtansine was compared to vinorelbine as second line therapy for MPM patients overexpressing mesothelin in a randomized phase II study (ClinicalTrials.gov identifier NCT02610140). The primary endpoint of this registration clinical trial is PFS. Moreover, a phase Ib trial of anetumab ravtansine combined with chemotherapy (cisplatin plus pemetrexed) to treat patients with cancers expressing mesothelin in first line setting is recruiting (ClinicalTrials.gov identifier NCT02639091).

To evaluate the potential synergism of check-point inhibitors with chimeric monoclonal antibody anti-

mesothelin, two phase I/II trials enrolling mesothelin-positive MPM patients were designed. The first phase I/II randomized trial will compare anetumab ravtansine plus pembrolizumab *vs.* pembrolizumab alone (ClinicalTrials.gov identifier NCT03126630). The second phase I/II trial will evaluate BMS-986148 administered alone and combined with nivolumab in patients with cancer over-expressing mesothelin (mesothelioma, NSCLC, ovarian cancer, pancreatic cancer and gastric cancer (ClinicalTrials.gov identifier NCT02341625).

CRS-207

CRS-207 is a recombinant, live-attenuated, double-deleted Listeria monocytogenes built to secrete mesothelin into the cytosol of infected antigen presenting cells (56).

A phase I trial demonstrated that CRS-207 was able to induce an immune activation and a mesothelin-specific T-cell response with a good toxicity profile (fever and chills or rigor) (57). Based on these results, a phase Ib study evaluating the activity and safety of CRS-207 combined with chemotherapy (cisplatin plus pemetrexed) in unresectable MPM patients was initiated (ClinicalTrials.gov identifier NCT01675765). CRS-207 was administered as maintenance for 2 more doses in responder patients. The combination resulted active, with a DCR of 94% (PR: 59%; SD: 35%) observed in 34 evaluable patients (58). Grade 1 chills or rigor (82%) and fever (79%) resulted as the most common toxicities. To evaluate the potential synergism of check-point inhibitors with anti-mesothelin vaccine, to evaluate safety and efficacy of CRS-207 with pembrolizumab in adults with previously-treated MPM a phase II trial was designed and it is currently recruiting participants (ClinicalTrials.gov identifier NCT03175172). RR is the primary endpoint of this trial.

Anti-MET drugs

The cMET receptor is a tyrosine kinase located on chromosome 7q31. Its ligand is represented by the hepatocyte growth factor/scattering factor (HGF/SF), a multifunctional growth factor regulating cell invasion, scattering and proliferation. The cMET receptor is able to activate multiple signaling pathways, including the Ras/Erk, PI3K/Akt, EGFR, IGF-1R, VEGFR, and c-Src kinase pathways, suggesting that multi-targeted approach may improve the activity of therapies against MPM (59,60).

In preclinical setting, overexpression of HGF/SF/cMET has been correlated with increased microvassel density and it was observed in a high percentage of MPM tissue compared with normal pleura (61-64). Moreover, the inhibition of cMET blocks cell growth in MPM cell lines but not in normal mesothelial cells (65).

Tivantinib

Tivantinib is an oral inhibitor of cMET. In preclinical model, tivantinib resulted able to suppress MPM cell proliferation and tumor growth in combination with PI3K/mTOR inhibitors (66).

A phase II trial evaluated the activity of tivantinib in 18 pre-treated patients with either pleural or peritoneal mesothelioma (ClinicalTrials.gov identifier NCT01861301). Among all the peritoneal mesothelioma patients, 43% of patients achieved stable disease for 9 months or more. Unfortunately, immunohistochemical MET expression or MET-mutation did not predict response to therapy in terms of DCR (67). Safety and tolerability of tivantinib combined with chemotherapy (carboplatin plus pemetrexed) in chemonaive patients with unresectable MPM or with advanced non-squamous NSCLC (EGFR wild type) is under evaluation in a phase I/II study (ClinicalTrials.gov identifier NCT02049060). Preliminary results showed that this combination is active in patients with lung cancer and safe (68).

Anti-FAK drugs

Asbestos fibers can induce chromosome and DNA damage in normal mesothelial cell and multiple genetic abnormalities, such as gain of function mutation or loss of tumor suppressor genes. The *BAP1* gene mutation and neurofibromatosis 2 type gene (*NF2*) loss represent the most important examples of genetic abnormalities which may have implications for therapy.

The *BAP1* is a tumor suppressor gene positioned on chromosome 3p21. Somatic mutations or 3p21.1 loss leads to *BAP1* inactivation. Approximately 40% of MPM patients have *BAP1* loss or mutation. The *BAP1* germline mutations can predispose patients to familial and sporadic mesothelioma, cutaneous/ocular melanoma, atypical melanocytic proliferations, and other internal neoplasms. In these individuals, asbestos exposure may predispose mesothelioma. The *BAP1* is a potentially involved in the modulation of histone modification. However, the activity of histone deacetylase inhibitors, such as vorinostat, resulted

poor in MPM patients (69).

The *NF2* gene is another tumor suppressor gene located on chromosome 22q12, encoding for the Merlin tumor suppressor protein. Approximately 50% of patients with MPM carry a loss of function of Merlin protein. Preclinical data indicate *NF2*-loss results in increased invasion and increased focal adhesion kinase (FAK) expression (70). FAK is a non-receptor tyrosine kinase that mediates growth-factor and adhesion-dependent signaling. In general, cells lacking expression of *NF2* products are susceptible to FAK inhibition.

Defactinib

Defactinib is an oral FAK inhibitor. In preclinical setting, it is able to decrement the number of cancer stem cells in malignant mesothelioma. Moreover, the inhibition of FAK was observed not only at the level of tumor cells but also on tumor-associated macrophages, inducing a decrease of cytokines (IL-6 and IL-8) release, responsible for cancer stem cells proliferation and survival (71). On the basis of these results, defactinib as maintenance therapy after first-line chemotherapy was evaluated in a randomized, placebo-controlled, phase II trial (the COMMAND trial; ClinicalTrials.gov identifier NCT01870609). The tumor merlin status was detected by immunohistochemistry prior to randomization. Unfortunately, the trial was stopped in October 2015 because unable to produce a sufficient level of efficacy. A phase II study evaluating defactinib in neo-adjuvant setting in patients with MPM candidates for surgery was done (ClinicalTrials.gov identifier NCT02004028). Preliminary results showed that defactinib is able to induce tumor volume reduction and tumor immuno-modulation (72).

Conclusions

Malignant mesothelioma is a rare disease with scarce therapeutic options. Moreover, there are several unresolved issues to suppress this aggressive disease, such as the lack of predictive biomarkers and adequate tools for response evaluation. It is too simplistic hope that a single "magic bullet" will be able to fight this aggressive disease. Therefore, it is mandatory to improve our knowledge of the MPM biology. To do it, we need to have sufficient archives of longitudinally collected serum, plasma, mononuclear cells, and paraffin blocks so that we can define genomic, proteomic, microRNA, or metabolomic differences between responders and non-responders for a given therapy. It should allow detection of prognostic or predictive biomarkers as well as induce the development of new therapeutic strategies. Unfortunately, several agents targeting the known molecular processes have proven ineffective in clinical trials and today, target therapy or chemotherapy alone achieved only poor results. Several reasons could explain this failure. Firstly, an erroneous strategy. Probably, to optimize the activity of target therapy it could be better to consider a multi-target therapy instead of mono-target therapy or to combine target therapy with chemotherapy. Considering the results of bevacizumab and nintedanib, the inhibition of angiogenesis in combination with chemotherapy seems to be a potential therapeutic strategy in this disease. Secondly, an erroneous selection of patients. In fact, the absence of EGFR and cKIT mutations conferring sensitivity to gefitinib in non-squamous NSCLC and to imatinib in gastro-intestinal soft tissue sarcomas, respectively, could justify the absence of activity of EGFR-, PDGFR- and cKIT-TKIs in MPM. Therefore, the identification of predictive biomarkers still remains mandatory. Thirdly, the choice of erroneous targets. Considering the high expression only on mesothelial cells, the inhibition of mesothelin with immunotherapy alone or in combination with chemotherapy represents an intriguing new target. Last but not least, multidisciplinary approach is mandatory to improve the management of this rare disease. The integration of preclinical studies into standard clinical practice is required to improve survival and quality of life of patients with MPM.

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None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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