REVIEW ARTICLE

Current and Emerging Therapy for Malignant Pleural Mesothelioma: Focus on CD26/Dipeptidyl Peptidase IV as a Therapeutic Target

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Abstract: ***Background***: Malignant mesothelioma is a largely incurable disease that is refractory to current therapies. CD26 is a multifunctional cell surface protein involved in autoimmune disease, diabetes, and cancer. It has a role in T cell function, extracellular protein modification, as a prognostic factor for cancer, and as a therapeutic target for malignant mesothelioma. New treatment strategies are urgently needed for malignant pleural mesothelioma (MPM), and CD26-targeted therapy represents a novel approach.

Outline: In this review, the most current and up-to-date literature available was reviewed and the current state of malignant mesothelioma treatment is described. Throughout the review the need for new therapeutic approaches is highlighted in the shortcomings of current therapy. CD26 is a target that is fit to take on these shortcomings. In this review we discuss the structure and function of CD26, its role in malignant mesothelioma and the future of anti-CD26 therapy as a versatile immunotherapeutic option.

Conclusion: This review highlights the areas of most promise in treating MPM, these include immune checkpoint blockade, passive immunization, and based on our recently published data, targeting of CD26 with its specific mAb. Finally we describe how the anti-CD26 mAb YS110 was recently evaluated in the first-in-human phase I clinical trial, showing prolonged disease stabilization and a favorable side effect profile. Through better understanding of CD26, new pathways to treating and potentially curing malignant mesothelioma may be discovered.

1. INTRODUCTION

The human leukocyte surface antigen CD26 is an active cell surface peptidase that is structurally identical to dipeptidyl peptidase IV (DPPIV), able to cleave N-terminal dipeptides from peptides with

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terminal L-alanine or L-proline residues (1-4). It is composed of 766 amino acids, the majority of which comprise the extracellular domain of the protein where a peptidase catalytic site is found and where important ligand binding sites for adenosine deaminase (ADA) and fibronectin are located [1-4]. The remainder of the protein structure includes a short 6-peptide cytoplasmic domain and a 23-peptide transmembrane region [4]. Through this peptidase activity CD26/DPPIV has significant effects on enhancing cellular response to external stimuli, effects on glucose homeostasis,

T cell stimulation and activation, and the biological behavior of selected human neoplasms. CD26 has relatively widespread expression on leukocytes, fibroblasts, mesothelium, endothelial, epithelial cells, and can be found in kidney, intestine, prostate, pancreas, and liver cells [5]. Since its discovery in 1966 by Hopsu-Havu and Glenner, CD26/DPPIV has been the focus of vigorous study in its pluripotent role in glucose homeostasis, inflammation, and more recently in tumorigenesis and as a therapeutic target in cancer [6]. The various immunomodulatory effects of CD26 have been previously summarized by our group and recently revisited and expanded by Klemann *et al.* [7, 8]. These works summarize the numerous substrates for DPPIV/CD26 and their far-reaching roles in autoimmune diseases such as multiple sclerosis, asthma, arthritis, and inflammatory bowel disease [7-9]. Likewise, CD26 involvement in malignancy has been extensively reviewed and characterized, including its potential role in terms of its role as a tumor suppressor, cancer biomarker, and therapeutic target [6, 10-14]. Additionally CD26 has been described as a marker for so-called cancer stem cells (CSCs) which have been a highly sought after targets in chemo-immunotherapy approaches [15]. Given the preponderance of evidence for CD26 involvement in various malignancies, as well as its role in immune activation and the biology of cancer stem cells, CD26 represents an ideal immunotherapeutic target; including for the aggressive, almost always fatal cancer malignant pleural mesothelioma (MPM).

Malignant pleural mesothelioma (MPM) is an aggressive and fatal disease. Over the past 60 years, since its acceptance as an independent oncological process, the incidence of MPM has continued to rise [16]. MPM is almost exclusively a direct result of exposure to asbestos [17]. Chronic pleural inflammation, ionizing radiation, and SV40 virus have been proposed as alternative exposures that can result in MPM, but these account for less than 20% of all cases [17]. Asbestos, a term for naturally occurring families of minerals that separate into thin fibers, has been used for greater than 5000 years for its high tensile strength and fire resistant properties [18]. It wasn't until the 1960s that the direct correlation between asbestos exposure and cancer development was validated and accepted [19]. Since that time, the WHO and International Agency for research in cancer have defined asbestos as a class I carcinogen responsible for both lung cancer and malignant pleural mesothelioma [18]. Inhaled asbestos fibers end up in the pleura, induce cytotoxic effects, and cause DNA damage and chronic inflammation [20]. This process is constant and smoldering for the next 20-60 years prior to the development of MPM. This long period of latency and protracted asymptomatic period explains the delayed peak in MPM cases and the increasing incidence over the past 40 years [21]. For example, in the US the peak in asbestos consumption occurred in the early 1970s, and its manufacturing was banned in the late 1980s, with total consumption and exposure risk being significantly reduced by the late 1990s; but the peak in MPM diagnoses of roughly 2,500-3,000 cases did not occur until about 2002 [22]. The expected plateau effect for MPM diagnoses for most industrialized nations that have banned the use of asbestos are expected to occur between 2015 and 2030, but countries like Russia, China, Brazil, and India continue to both mine and use asbestos at an alarming rate [23]. China has become the worlds largest asbestos-consuming country, has little to no reporting mechanism of its MPM rates, and will likely experience a surge in MPM diagnoses in the future [24]. With this predictable man-made epidemic looming on the horizon, new strategies are required for treating this aggressive disease as current strategies show limited efficacy, poor survival benefit, and have significant morbidity associated with them [18]. In this review, we will discuss the current state of malignant mesothelioma treatment and some of the burgeoning therapies currently in clinical trials. We will also highlight the work done on CD26 expression in MPM, its potential as a biomarker, and its functional role in MPM survival, invasion, and migration. Finally, we will review the ongoing clinical development of an anti-CD26 monoclonal antibody in malignant mesothelioma and its potential far-reaching implications as a novel immunotherapeutic agent.

2. CURRENT THERAPIES

If left untreated, MPM has an average life expectancy of 8 months and a 5-year mortality of greater than 95% [24]. Our best efforts with multimodal therapy may extend this outcome by mere months, further emphasizing the extreme need for improved therapies. Current therapeutic strategies

Table 1.   Principal characteristics and benefit of current therapies for MPM.

First Line Therapy	Overall Survival (Months)	Improvement *vs.* SOC	Study Features/ Limitations	References
None	8	n/a	Na/	Zhang *et al.* Ann Transl Med 2015
Cisplatin + pemetrexed (SOC)	16.1	0	225 pts, newly diagnosed MPM, ECOG 0-2	Zalcman *et al.* Lancet 2016
SOC + bevacizumab	18.8	2.7	223 pts, newly diagnosed MPM, ECOG 0-2	Zalcman *et al.* Lancet 2016
SOC + EPP	21.9	5.8	54 pts, stage I to III MPM, otherwise healthy, ECOG 0-1	Krug *et al.* J clin oncol 2009
EPP + IMRT	14.2	None	63 pts, able to tolerate EPP, minimal comorbidities	Rice *et al.* Ann thorac surg 2007
EPP + SOC + hemithoracic RT	29.1	13	42 pts, ECOG 0-1, T1-3 N0-2 (33 pts who entered study could not tolerate all phases of therapy)	Krug *et al.* J clin oncol 2009
PD + SOC + IMPRINT	20.2	4.4	70 pts, retrospective study over 30 years, high karnofsky score	Shaikh *et al.* J of thoracic oncol 2017
CRS-207 + SOC	8.5*	N/A	38 pts, treatment naïve, ECOG 0-1	Jahan *et al.* J of thoracic oncol 2016

Second Line Therapy	Overall Survival (Months)	Improvement *vs.* Historic Chemo	Study Features/ Limitations	Reference
Tremelimumab + SOC	10.7	2.0	29 pts, ECOG 0-1, primarily epithelioid histology	Calabro *et al.* Lancet Respir Med 2015 MESOT-TREM-2012

Abbreviations: MPM (Malignant Pleural Mesothelioma), ECOG (Eastern Cooperative Oncology Group Performance Status), SOC (Standard of Care), pts (patients), EPP (Extrapleural Pneumonectomy), PD (Pleurectomy with Decortication), IMRT (Intensity-modulated Radiation Therapy), CRS-207 (live, attenuated, double-deleted listeria monocytogenes engineered to express tumor-associated antigen mesothelin).* (progression free survival, overall survival goal not met to date).

for MPM include surgery, radiation, chemotherapy, and more recently targeted therapy and immunotherapy [25-31]. Table **1** summarizes the mainstays of treatment and the benefit of traditional therapies over systemic chemotherapy. The roles of surgery and radiation as part of MPM treatment are rife with controversy, with these modalities showing limited benefit in patients with advanced disease.

2.1. Multimodal (Surgical Resection, Radiotherapy, and Chemotherapy)

Surgical intervention is difficult to perform, since achieving negative margins when extracting thin areas of pleura is difficult to accomplish and is associated with a significant level of risk, requiring a high level of familiarity and expertise with the procedure [32]. Two main surgical interventions are currently in use, pleurectomy/decortication (P/D) and Extrapleural Pneumonectomy (EPP) [29]. As illustrated in the MARS trial, EPP, an invasive aggressive debulking procedure showed no benefit when added to chemotherapy/radiation, being associated with a worse median survival when compared with no surgical intervention, and may actually cause harm [33, 34]. However, it is important to note that this study, like many involving MPM, is extremely underpowered and involved only 19 individuals re-

ceiving EPP [34]. With the high morbidity and required technical expertise, this procedure has therefore fallen out of favor except in those patient fortunate enough to be diagnosed at an early-localized stage.

P/D is being evaluated currently in the MARS2 trial to evaluate the role of surgery in MPM therapy, aside from its value in diagnostic biopsy [32]. In a similar vein, radiotherapy has been used in combination with chemotherapy and surgery as part of a trimodal therapeutic approach, or following surgery to prevent tumor seeding of thoracoscopy or thoracotomy scars. Trimodal therapy involves chemotherapy followed by EPP or P/D and intensity modulated radiotherapy as combination treatment for MPM. Results from small trimodal clinical trials suggest that, in certain patient populations, this aggressive multipronged attack may improve overall survival by up to 6 months *vs.* standard of care (SOC) [35]. However, this treatment option is only valuable to those MPM patients with limited burden of disease, excellent performance status, and epitheliod histology [36]. While surgery and radiotherapy may have some role to play in specific MPM cases, the mainstay of treatment for the past 20 years has been systemic chemotherapy.

2.2. Systemic Chemotherapy in Malignant Mesothelioma (SOC)

For a prolonged period of time, there was no consensus as to the optimum systemic chemotherapy used for MPM due to the limited randomized clinical trial data to support one strategy over another. It is important to mention that systemic chemotherapy for MPM is palliative in nature and has been the only intervention to show modest improvement in overall survival [27, 37]. This situation changed in 2003 following the availability of the results of the EMPHACIS phase III trial, which showed the superiority of the combination of cisplatin and pemetrexed over cisplatin alone, which was the most commonly used first line chemotherapy at the time [38, 39]. In this study, median survival was improved from 9.3 to 12.1 months [39]. These data led to the formal approval of the pemetrexed/cisplatin combination as the new SOC for MPM, a development which has not changed in the decade plus since it was first described [37]. Additional studies have validated the use of a different antifolate, raltitrexed, with

cisplatin as an appropriate alternative regimen if pemetrexed is not well-tolerated [40]. Many clinicians also substitute carboplatin for cisplatin to reduce toxicity with little clinical difference in outcomes and without formal FDA approval [41]. Meanwhile, the recently published MAPS study demonstrated the clinical benefit of adding bevacizumab to SOC which resulted in an additional 2.7 month survival benefit though not without risks as the bevacizumab arm had higher reported adverse events across multiple subgroups and significant increases in grade 3-4 arterial and venous thromboembolic events [42]. However, even with this increase in median survival from the addition of bevacizumab plus SOC, MPM typically recurs as an incurable disease, necessitating the development of effective second line therapeutic options. Unlike the case with first line therapy, there is currently no established SOC therapy for disease recurrence or progression following initial management. The most common second line chemotherapy options include the vinca alkaloid vinorelbine, the anti-nucleoside analog gemcitabine, and the re-administration of single agent pemetrexed, which have shown the most promise in terms of tolerability but have failed to improve overall survival [27, 43]. In view of these shortcomings of currently available therapies, novel treatment strategies including targeted strategies and immunotherapy have been explored as both adjunctive and independent options for systemic therapy of MPM.

2.3. Targeted Therapies and Immunotherapy in Malignant Mesothelioma

Given the overwhelming lack of second line options in MPM and the large percentage of patients diagnosed with advanced disease that is not amenable to aggressive multimodal approaches, there has been a focus on targeted therapies with biological agents over the last 10 years, albeit with mostly disappointing results. Targeting various tyrosine kinases and the process of angiogenesis, as well as representing various forms of immunotherapy, these therapies can be broadly subcategorized into small molecule inhibitors, angiogenesis inhibitors, histone deacetylase (HDAC) inhibitors, and gene mutation targeting. The small molecule inhibitors include multitargeting receptor tyrosine kinase inhibitors (mTKIs), selective tyrosine kinase inhibitors (sTKIs), and

proteasome inhibitors. These molecules have garnered much focus in the oncologic world with broad applications in both solid and liquid tumors [44-47]. Unfortunately, phase I and phase II clinical trials involving the mTKIs sorafenib, sunitinib, pazopanib, and desatinib showed either limited anti-mesothelioma activity, the inability to induce remission, and/or unacceptable toxicity [48-52]. These receptor tyrosine kinase inhibitors broadly target EGFR, VEGFR, PDGFR, and C-kit to exert their anticancer effects. While these self-signaling molecules are upregulated in MPM, they do not appear vital to its propagation and are not MPM specific, which likely contributes to the limited efficacy of these drugs. Interestingly, the process of angiogenesis has only been successfully targeted by the monoclonal antibody bevacizumab and not by the above mentioned mTKIs which target VEGFR, or by the biologic agent thalidomide which primarily works through angiogenesis inhibition [53, 54]. Thalidomide was tested in clinical trials as both adjunct to standard of care treatment and as maintenance therapy for MPM patients previously treated with platinum based chemotherapy. The results of these studies showed no benefit to thalidomide as adjunct and no improvement in overall survival (OS) *vs* supportive care alone as maintenance therapy [27, 54]. Guazelli *et al.*, recently summarized active phase I and phase II clinical trials and highlight that many studies have looked at targeting the EGFR or VEGR pathway with little success to show for it up to this point, this review expertly highlights the current clinical trials that are ongoing from Clincaltrials.gov [53]. Since EGFR expression is upregulated in the majority of MPM, selective tyrosine kinase inhibitors like erlotinib and gefitinib should theoretically exhibit increased activity against MPM. Unfortunately, similar to the mTKIs, results from phase II clinical trials were disappointing. Limited efficacy and marked resistance to these sTKIs was observed even in the presence of detectable EGFR expression on MPM tumors [55-57]. Similar results to these were seen with the proteasome inhibitor bortezomib, which has been approved for use in multiple myeloma and is currently in clinical trials for multiple other cancers including non-small cell lung cancer and metastatic breast cancer [58]. In two different clinical trials bortezomib failed to show objective response as monotherapy and failed to provide significant OS survival or disease progression benefit when combined with SOC [59].

HDAC inhibitors, specifically vorinostat, which modify and limit deacetylation of histone and block access genes that are overused by cancer cells for progression and division, showed promising results in early clinical trials [60]. These results prompted the large-scale VANTAGE-014 phase III double blind, randomized placebo control study using vorinostat monotherapy as either second- or third-line therapy for MPM [61]. Results reported in the Lancet in 2015 of this large well designed and well executed study (660 patients enrolled) showed no benefit to vorinostat over placebo in terms of overall survival [61]. Gene mutations have been a hallmark of targeted cancer therapy, but few highly conserved gene mutations in MPM have been identified, and studies involving those found and targeted have failed to result in clinically significant efficacy. The most common mutations observed through molecular genetic analysis of patient MPM samples include BAP1, PTEN/PI3K, CDKN2A/ARF, and NF2 [62-65]. Of these, NF2 has been identified in 40% of MPM and results in inactivation of a protein called Merlin which is involved in cell adhesion and motility. Of potential therapeutic value is the fact that Merlin loss increases cell sensitivity to focal adhesion kinase (FAK) inhibitors [66]. Initial research showed FAK inhibitors, specifically defactinib, along with their MPM cytotoxic effect reduced so called cancer stem cell populations in MPM with potential for more durable prolonged response *vs* SOC [66]. These results prompted a large phase II COMMAND study which enrolled 372 patients to receive defactinib plus SOC *vs* placebo plus SOC control arm as first line therapy for MPM [67]. Unfortunately as is often the case in MPM clinical trials, the study was stopped during recruitment when no difference in defactinib *vs* placebo were observed, even when subdivided to those patients with identifiable merlin loss [68].

Immunotherapy has been on the forefront of cancer therapy for the past 20 years and recent successes in immune checkpoint inhibition, tumor escape mechanism targeting, passive immunotherapy, and dendritic cell vaccines have pushed the field further with ever broadening application [69-71]. Recent advances in immunotherapy and current clinical trials in MPM are well summarized by

Thapa *et al.*, [72]. In their review of current immunologic strategies, the failures of targeting MPM with single agent immunotherapy warrants the use of combination strategies to improve efficacy [72]. One of the more successful pathways of immunotherapy described in their work and others is the use of immune checkpoint inhibition as a novel target in MPM [72]. An example of immune checkpoint inhibition is the strategy of targeting and blocking CTLA-4. CTLA-4 is a cell surface co-factor expressed on the surface of T cells that acts as an inhibitory cofactor for CD80 and CD86 [73]. CTLA-4 competes with CD28 for binding with CD80/86 and when bound sends an inhibitor signal to antigen presenting cells to decrease the inflammatory response and diminish cell activation. This process allows CTLA-4 to protect surrounding cells and the system as a whole from uncontrolled immune stimulation [74]. Tumor cells, including malignant mesothelioma, express increased level of CTLA-4 as a means of blocking anti-tumor immune responses [74]. Inhibition of CTLA-4, or so-called checkpoint inhibition, therefore can restore the anti-tumor immune response, resulting in T cells recognition and attack of tumors that had previously been undetected. In a recent review, Guazelli *et al.* have summarized the role of CTLA-4 targeting in MPM [75]. They and others point out monoclonal antibodies (mAb) directed against CTLA-4 have shown impressive results in melanoma and have been tested in early clinical trials with MPM [75]. The CTLA-4 mAb Tremelimumab has been investigated in the MESOT-TREM-2008, and MESOT-TREM-2012 phase II clinical trials in patients with chemotherapy-resistant MPM [28, 75, 76]. In these studies, Tremelimumab treatment resulted in a disease control rate of 31% when administered every 3 months, and a control rate of 52% when given every 4 weeks, a regimen that led to improved efficacy in other cancers [75-77]. Furthermore, with the shorter dosing time, median OS was improved to 10.7 months compared to historical averages of 8.7 months with second line chemo [77]. These early results have led to an ongoing study comparing Tremelimumab monotherapy *vs* placebo control. Additionally, combination immunotherapies, CTLA-4 blockade combined with anti-PD-L1 therapy is under active investigation and was recently presented at ASCO 2016 with the combination of Tremelimumab and durvalumab

[75]. Like CTLA-4, programmed death ligand 1 (PD-L1) is overexpressed in MPM, particularly the sarcomatoid type, and exerts an inhibitory effect on T cells to suppress the anti-tumor immune response [77]. Binding PD-L1 with ligand specific mAbs therefore blocks this tumor escape mechanism, potentially resulting in greater susceptibility of MPM to immune destruction. In the recent KEYNOTE-028 phase I clinical trial, the PD-1 mAb pembrolizumab was tested in a 25 patient cohort and showed an impressive overall disease control rate of 76% [73, 78]. This has prompted larger phase II investigation to further explore the anti-MPM activity of pembrolizumab [73].

Additional passive immunotherapy strategies in MPM have focused on targeting the tumor-associated antigen Mesothelin. Mesothelin expression is increased in MPM and likely plays a role in cell adhesion and invasion [79, 80]. Strategies focusing on mesothelin targeting have involved the mAb Amatuximab, anti-mesothelin vaccine CRS-207, and the mAb-toxin fusion protein called SS1P [79]. Amatuximab is a chimeric anti-mesothelin mAb that was tested in a phase II multicenter trial of 89 MPM patients in combination with SOC (pemetrexed/cisplatin) *vs* SOC alone, with improved OS in the Amatuximab-containing arm [81]. The anti-mesothelin vaccine CRS-207 is a live, attenuated, derivative of listeria monocytogenes that expressed the mesothelin Ag and activates both innate and adaptive immunity [82]. The synergistic effects of CRS-207 and SOC chemotherapy was tested in a phase I trial of 38 MPM patients which showed encouraging anti-tumor immunity, with a progression free survival of 8.5 months [82]. Encouraging results from this study has led to a large multicenter phase III clinical trial that is currently recruiting. Similarly, the recombinant anti-mesothelin and truncated pseudomonas exotoxin SS1P has shown significant anti-tumor activity and tolerability in a phase I clinical trial [83]. Finally, adoptive transfer of *ex vivo* stimulated dendritic cells, so called dendritic cell vaccination has recently shown activity in MPM. In a trial of 10 patients with MPM, cyclophosphamide was given to reduce activity of T regulatory cells prior to infusion of dendritic cells pulsed with autologous tumor lysate [84]. Results of this small study showed radiographic disease control in 8/10 patients and an impressive OS of greater than 2

years in 7/10 patients [84]. This technique will likely be expanded and further investigated in future years.

3. POTENTIAL APPROACH TO TARGETING CD26 IN MPM

As discussed above, treatment for MPM beyond first line therapy is still unsatisfactory due to limited efficacy, and novel therapeutic approaches are urgently needed for this patient population. While immunotherapy approaches appear promising with encouraging efficacy in multiple small studies, the observed benefit is still relatively short lasting and typically limited to only a few months. Additionally some concerns that arise with all studies involving immunotherapy include utilizing progression free survival (PFS) *vs* OS as an overall marker of drug efficacy or combining drugs that lack single-agent activity. In a recent study published in the Journal of Clinical Oncology, Tan *et al.* performed a meta-analysis of trials with results posted on ClinicalTrials.gov where they found a majority of studies showing significant benefit on PFS but not on OS [85]. They highlight the need for studies to look at both PFS and OS and to not use one as a surrogate marker for the other [85]. In separate commentary, Gyawali and Prasad illustrate that multiple trials over the past decade where multiple drugs without proven single-agent efficacy were added together as a novel treatment and showed PFS but rarely showed an effect on OS [86]. They pose in additional manuscript that by combining multiple therapies to extent PFS we run the risk of subjecting patients to unnecessary side effects and risks for little benefit [87]. These compelling examples shed light on the grain of salt mentality that is needed when evaluating the efficacy of immunotherapy. Unfortunately, as is usually the case, most of these trials and analysis did not include studies involving MPM. Given the small treatment arms and aggressive nature of MPM small gains in PFS may indicate improvement in OS but the low power of these studies makes statistical extrapolation difficult and with such a short OS window for these patients even small gains should be looked at as possible treatment strategies. There studies confirm and support the need for improved targeting in diseases like MPM and stresses the importance of single-agent efficacy in therapy design before a drug is pushed forward through clinical trials and towards FDA approval. Thus, an ideal target in MPM would be one that is highly expressed by malignant mesothelioma cells but absent from normal mesothelioma, and plays a role in tumor proliferation or invasiveness. In addition, therapy specifically targeting this antigen should work in concert with chemotherapy to enhance treatment efficacy without increasing side effect burden, have strong activity as a single agent, and improve both PFS and OS in MPM patients. All these characteristics can be found potentially in the surface antigen CD26.

3.1. CD26 Expression and Function in MPM

CD26 is a multifunctional cell surface receptor with roles in immune regulation, T cell activation, and malignant potential of various cancers. CD26 is highly expressed in MPM and was originally identified as a potential target by our group [88, 89]. Our initial work demonstrated that targeting CD26 with anti-CD26 mAb resulted in *in vitro* growth inhibition of MPM cell line [89]. Subsequently, we showed high CD26 expression on various human MPM types including localized MPM, well-differentiated papillary MPM, and diffuse MPM but not on adenomatoid tumors or reactive mesothelioma cells [88]. Complementing our earlier *in vitro* work, we also demonstrated for the first time the potential for targeting CD26 in MPM with anti-CD26 mAb in an *in vivo* NOD-SCID mouse model of MPM. This initial evaluation for CD26 expression on a small sample population of MPM tissues was then further expanded in a follow-up paper which demonstrated overexpression of CD26 in MPM in more than 120 different MPM surgical samples including epitheliod mesothelioma, biphasic mesothelioma, and sarcomatoid mesothelioma as well as 8 different mesothelioma cell lines [90]. Interestingly, the more aggressive sarcomatoid mesothelioma samples had reduced cell surface CD26 expression but retained cytoplasmic CD26 expression. This work suggested that the morphology of the mesothelioma cell type, which has been used as a prognostic factor in the disease, correlated with CD26 expression and that loss of membranous CD26 was associated with the more aggressive spindle shaped sarcomatoid mesothelioma, raising the possibility that the loss of CD26 in these cells represented an epithelial to mesenchymal transition for MPM potentially responsible for the difficulty in treating and poorer

outcome associated with sarcomatoid MPM [90]. We subsequently showed that CD26 surface expression was associated with improved survival in MPM patients that received chemotherapy and potentially contributed to mesothelioma chemosensitivity [91]. We also demonstrated through *in vitro* investigation that CD26 was associated with enhanced proliferative activity of MPM and through downstream gene activation, CD26 upregulated mechanisms that increased chemotherapy sensitivity [91]. Given the increased surface expression of CD26 in favorable MPM phenotypes, soluble CD26 (sCD26) was investigated as potential biomarker for MPM. We showed in a recent preclinical model of MPM that sCD26 levels were higher in patients with the favorable epitheliod phenotype than those with the aggressive sarcomatoid subtype and through therapeutic monitoring, reduction in sCD26 may indicate progression of disease [92]. Whether sCD26 can be used in high-risk patients, those with previous significant asbestos exposure or those residents of asbestos mining communities, as a screening tool for early detection of disease remains to be determined. Additionally, CD26 expression was identified and characterized as a marker for so called cancer stem cells (CSC) in MPM and was found to be co-expressed with the CSC marker CD24 [93]. In this study we used shRNA knockdown of CD24 and CD26 to determine the effects of gene silencing in the MPM cell line Meso-1 [93]. We showed that through silencing of CD26 but not CD24 MPM cellular invasion was reduced and MPM showed reduced proliferation [93]. Gene knockout of CD26 additionally caused an reduction in the cancer cell signaling molecules IGFBP7, IGFBP3, Wnt5A, and IL7R [93]. These studies also showed CD26 played a role in asymmetric cell division and invasion potential in MPM cell lines [93]. These collective works clearly validated CD26 as a surface receptor upregulated in MPM with various roles in cell proliferation, invasion, and chemosensitivity, while loss of expression correlated with progression of MPM to a more aggressive treatment-resistant phenotype.

These studies on CD26 expression in MPM were subsequently followed by our work evaluating molecular mechanisms for CD26 role in cellular invasiveness. We showed that CD26 promotes invasiveness through the formation of CD26-α5β1 integrin molecular complexes that interact with various cell surface and endothelium receptors and stimulate extra-cellular matrix metalloproteinases [94]. In addition, the short 6 amino acid cytoplasmic region of CD26 plays a crucial role in MPM migration and invasion through upregulation of periostin [95]. We demonstrated that the lipid raft platforms clustered around CD26, indirect activation and phosphorylation of the proto-oncogene Src occurred resulting in nuclear translocation of the transcription factor Twist1 [95]. Through this mechanism, periostin production is increased, associated with an enhancement in the migratory potential and invasiveness of MPM, contributing to both progression of disease and metastases. CD26 therefore represents a targetable MPM specific molecule with a direct role in the invasiveness and metastatic potential of MPM.

3.2. CD26 Targeting in Malignant Mesothelioma

As mentioned above, proof-of-concept studies using preclinical MPM models demonstrate that targeting CD26 with its specific mAbs is a viable anti-cancer therapeutic approach. Treatment of MPM cell lines with the humanized anti-CD26 mAB, YS110 resulted in p27^{kip1} accumulation leading to cytotoxicity in both *in vitro* and *in vivo* models [88]. Binding of YS110 also had a direct role in regulating binding to extra-cellular matrix proteins, biphasic antitumor immunity through immune activation and direct cytotoxicity, as well as inhibition of distant metastases [88]. In addition, anti-CD26 mAB enhanced nuclear translocation of CD26 with downstream effects resulting in mesothelioma growth suppression [96, 97]. Cellular localization analysis revealed that YS110 caused an increase in transport *via* caveolin-dependent endocytosis and accumulation of CD26 to the nucleus of MPM resulting in suppression of POLR2 gene expression and subsequent growth suppression of MPM cells, while highlighting a secondary anti-tumor mechanism of anti-CD26 mAbs [96, 97]. Meanwhile, a recently published paper demonstrated that YS110 caused retarded G2/M cell cycle progression through inhibition of phosphorylation of cdc2 and cdc25C and activation of ERK1/2 [98]. Importantly, a synergistic effect between YS110 and the first line anti-MPM chemotherapeutic agent pemetrexed was observed, as the combination of YS110 and pemetrexed showed superior anti-tumor activity associated with combinatorial G1/S and G2/M cell cycle tran-

sition inhibition than either agent alone in a mouse xenograft model of MPM [98].

These encouraging preclinical results along with our increased understanding of the novel molecular mechanisms involved in CD26 targeting in cancer cells led to the first-in-human phase I study of YS110 in CD26 expressing cancer cells. This recently published study involved 33 patients with CD26+ tumors (22 of whom had heavily pre-treated MPM) treated with a standard 3+3 escalation scheme with escalating doses of YS110 [99]. YS110 was generally well tolerated even to doses of 6mg/kg weekly, with maximal tolerated dose not reached and only 2 patients reporting grade 3 or higher anaphylactic or allergic reactions, which entirely resolved with supportive treatment and dose omission [99]. When the study was subsequently amended to add clinically relevant allergies as a new exclusion criterion and to allow for the administration of a systemic steroid prophylaxis prior to each infusion to better control infusions reactions, the safety profile was even further improved with treatment doses being escalated to 6mg/kg without dose limiting toxicities. While there was a transient decrease in total peripheral lymphocyte counts and CD26+ lymphocyte subsets following antibody administration, there was no observed autoimmune or infectious disease occurrences [99]. Furthermore, in this first-in-human phase I study, prolonged disease stabilization was observed in a significant number of patients that received YS110 [99, 100]. Thirteen of 26 evaluable patients treated with YS110 had stable disease as the best response for an overall median PFS of 43 days, while 7 patients (including five cases of mesothelioma) experienced prolonged PFS of 184-399 days [99, 100]. Taken together, data from both preclinical studies as well as the recently completed first-in-human phase I clinical trial indicate that additional testing of YS110, which may represent a major breakthrough in the treatment of MPM, in future clinical trials as either single agent therapy or as part of combination therapies with other anti-neoplastic agents, would be warranted.

CONCLUSION

MPM is an ongoing oncological concern. With continued mining and use of asbestos globally in developing countries and major industrialized nations like China and Russia, MPM cases will predictably increase in the coming decades. When found, treatment strategies include combination surgery, radiation, and chemotherapy; although few patients are diagnosed in time to benefit from definitive surgery, with systemic chemotherapy being thus left for many patients as their only option. While beneficial at reducing symptoms, systemic chemotherapy with pemetrexed and cis-platin (SOC) fails to provide curative benefit for most MPM patients and only extends overall survival by a matter of months. The addition of novel biologic agents such as bevacizumab to standard of care will likely provide modest survival benefit but has yet to become the approved standard. For most patients with MPM, following initial systemic therapy, disease commonly relapses with progression and metastases. Over the past 20 years, many chemo- and immunotherapeutics have been evaluated as potential treatments for MPM with limited benefit. Novel immunotherapy strategies including passive immunotherapy, mesothelin targeting, and checkpoint inhibition targeting have recently shown promise in small phase I and II studies. In this review, we highlight the need for novel therapeutic approaches in MPM and discuss the potential of CD26 as a new molecular target. CD26 is highly expressed in MPM with limited expression in normal mesothelial cells. Unlike other immunotherapeutic targets, CD26 has a direct role in progression, invasion, metastasis, and cancer-stem cell proliferation in MPM. Our recently completed first-in-human phase I clinical trial involving the anti-CD26 mAb YS110 suggests that successful targeting of CD26 may lead potentially to improved disease control and prolonged overall survival with limited toxic side effects in malignant mesothelioma. The successful development of a CD26-targeted approach will enhance the treatment armamentarium available against MPM as we prepare for this predictive epidemic.

LIST OF ABBREVIATIONS

DPPIV   =   Dipeptidyl Peptidase IV

MPM   =   Malignant Pleural Mesothelioma

mAb   =   Monoclonal Antibody

SOC   =   Standard of Care

CSC   =   Cancer Stem Cells

OS   =   Overall Survival

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

Nam H. Dang, Chikao Morimoto, and Kei Oh-numa are stockholders of Y's AC Co, Ltd.

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