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MINI REVIEW

Review on clinical trials of targeted treatments in malignant mesothelioma

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Abstract
Purpose Malignant mesothelioma (MM) is an aggressive tumor of the serosal surfaces with a poor prognosis. Advances in the understanding of tumor biology have led to the development of several targeted treatments, which have been evaluated in clinical trials. This article is a comprehensive review of all clinical trials evaluating the effect of targeted treatments in MM.
Methods An extensive literature search was performed in January 2011 using pubmed and medline. No constraints on publication date were applied.
Results Thirty-two trials exploring 17 different targeted agents in MM were found. Treatment in first- and second-line targeted agents induced response rates ranging from 0–14% and 0–16%, respectively. The tyrosine kinase inhibitor sunitinib induced partial response in 10% and stable disease in 66% of MPM patients as second-line treatment. A preliminary analysis of a phase II/III trial suggests that addition of bevacizumab to pemetrexed and cisplatin first-line treatment significantly improves disease control (CR + PR + SD) in the bevacizumab arm (73.5%) compared with treatment with pemetrexed and cisplatin without bevacizumab (43.2%) ($P = 0.010$). Another phase II trial did not observe any significant clinical benefit of adding of bevacizumab to gemcitabine and cisplatin.
Conclusions Disease stabilization is reported in some patients with several targeted treatments and might be beneficial in subgroups of patients or in combination with classic chemotherapy. None of the hitherto explored targeted treatments can currently be recommended as standard treatment in MM.

Keywords Malignant mesothelioma · Malignant pleural mesothelioma · Targeted treatments · Tyrosine kinase inhibitors

Abbreviations

ABL	Abelson murine leukemia viral oncogene homolog
AKT	A member of the non-specific serine/threonine-protein kinase family
ALK	Anaplastic lymphoma kinase
BCR	Breakpoint cluster region
CALGB	Cancer and leukemia group B
c-KIT	V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
CML	Chronic myeloid leukemia
CR	Complete response
EGF	Endothelial growth factor
EGFR	Endothelial growth factor receptor
EML4	Echinoderm microtubule-associated protein-like 4
EPP	Extrapleural pneumectomy
FDG-PET	Fludeoxyglucose(18F) positron emission tomography
GIST	Gastrointestinal stromal tumor
HDAC	Histone deacetylase
HDACi	Histone deacetylase inhibitor
IFP	Interstitial fluid pressure
IGF-1	Insulin-like growth factor 1
KDR	Kinase insert domain receptor
MM	Malignant mesothelioma
MPM	Malignant pleural mesothelioma

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mTOR	Mammalian target of rapamycin
NGR	Asparagine–glycine–arginine
hTNF	Human tumor necrosis factor-alpha
OS	Overall survival
PD	Progression disease
PDGF	Platelet derived growth factor
PDGFR	Platelet derived growth factor receptor
P/D	Pleurectomy/decortication
PFS	Progression free survival
PI3K	Phosphatidylinositol 3-kinase
PR	Partial response
RNA	Ribonucleic acid
SRC	Sarcoma
SD	Stable disease
TGF-alpha	Tumor growth factor-alpha
TKI	Tyrosine kinase inhibitor
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

Introduction

Malignant mesothelioma (MM) is a rare malignancy, most commonly located to the pleura (malignant pleural mesothelioma (MPM)) (90%), or peritoneum (less than 10%). Around 75% of patients have been exposed to asbestos with a latency period around 20–40 years. Adverse prognostic factors are non-epithelioid histological subtype, advanced stage, poor performance status, low hemoglobin level, leucocytosis, and thrombocytosis [1]. Patients with sarcomatoid and mixed histology tend to die within 10–12 months of diagnosis, whereas those with epithelioid histology tend to survive a few months longer [2].

Multimodality treatment including radiation therapy, surgery and chemotherapy is an option for some MPM patients with limited disease extension. Although MM has a low tendency to metastasize, MM grows highly invasive into surrounding tissue. The invasive growth is related to high levels of expression of matrix metalloproteinases that are able to degrade both basement membrane and stromal extracellular matrix components [3]. A systemic treatment is the main therapeutic option for most patients due to the invasive behavior and limited efficacy of radiation therapy.

Most experience on medical treatment of MM originates from trials on MPM. Current treatment of MPM includes chemotherapy with response rates around 20–40%, progression free survival (PFS) from 5.3 to 8.9 months, and median overall survival (OS) between 9 and 15 months in chemotherapy naïve patients [4]. The most active first-line regimens are platinum compounds together with another active agent such as pemetrexed, raltitrexed, gemcitabine, or vinorelbine. A much used combination of cisplatin and pemetrexed has yielded response rates (RR) of 41.3%, median OS of 12.1 months, and median PFS of 5.7 months in a randomized trial [5].

Most patients with MPM progress during or shortly after first-line treatment and second-line treatments are frequently used in this setting. There is no standard second-line treatment in MPM although pemetrexed has been suggested to pemetrexed naïve patients due to studies reporting RR of 5.5–32.5%, PFS of 3.8–7.4 months, and OS of 4.1–9.8 months. Various second line chemotherapy regimens in pemetrexed pretreated patients have yielded RR of 7–11%, PFS of 2.2–3.5 months, and median OS of 5.9–10.9 months [6]. Due to the limited efficacy of chemotherapy, new treatment options are clearly warranted and several targeted agents have thus been explored. Accordingly, we reviewed the current status of targeted treatment in MM.

Materials and methods

An extensive literature search was performed in January 2011 using pubmed and medline. Articles using targeted agents in malignant mesothelioma and providing clinical details, patient characteristics, treatment and outcome were qualified for inclusion in the review. Keywords used were combinations of, "mesothelioma", "targeted treatment", "biological treatment", "molecular targets", and "tyrosine kinase inhibitor".

Reference lists in relevant articles were also used. ASCO abstracts from 2009 and 2011 were included as it was assumed that earlier abstracts have been published. In the case of phase I trials, only data relevant to malignant mesothelioma have been mentioned. Full tables of all clinical trials discovered are displayed. Data on ongoing trials were derived from http://www.clinicaltrials.gov.

Results

Drugs have been listed according to their target. As for multikinase inhibitors, the drug has been listed according to the most relevant target.

Platelet-derived growth factor/platelet-derived growth factor receptor (PDGF/PDGFR) (Table 1)

PDGF (platelet-derived growth factor receptor) is a growth factor inducing mesothelial cell proliferation. The PDGF-alpha receptor is known to be overexpressed on mesothelioma cells. Increased secretion of PDGF is thought to cause the thrombocytemia, which is known to be an

Table 1 Targeted treatment with tyrosine kinase inhibitors in non-resectable malignant mesothelioma patients

Author	Agent	Phase	Primary tumor	Histology	Previous systemic treatments	No. of pts.	Res. (%)	mPFS (months)	mOS (months)
Drugs targeting PDGFR									
Villano et al. [13]	Imatinib	II	Pleura (94%), Periton (6%)	E (80%) B (20%)	Prior chemo ($n = 16$)	17	0	1.7	NA
Porta et al. [12]	Imatinib	II	NA	E (72.2%) S (0%) B (27.2%)	None (22.2%) Other (81.8%)	11	0	2	5
Mathy et al. [11]	Imatinib	II	Pleura (92%) Periton (8%)	E (80%), S (4%) B (12%) N/A (4%)	None ($n = 23$), Suramin ($n = 1$) Thal ($n = 1$)	25	0	NA	13.2
Millward [10]	Imatinib	II	NA	NA	Prior chemo ($n = 7$) Cis/Carbo ($n = 6$) Gem ($n = 4$) Pem ($n = 2$) Vnb ($n = 2$)	29	0	NA	NA
Yaqoob [16]	Imatinib + Gem	I	NA	NA	NA	5	20	NA	NA
Tsao [20]	Dasatinib	[a]	NA	E (87%), B (13%)	None	15	0	NA	NA
Dudek [21]	Dasatanib	II	Pleural (76%)	E (72%)	Pem 100%	46	0	2	4,8
Janne [24]	Sorafenib	II	Pleural (90%) Peritoneal (10%)	E (37%), S (4%) B (8%) N/A (2%)	None ($n = 20$) or Pem ($n = 31$)	51	4	3.7	10.7
Irshad [23]	Sorafenib	II	NA	NA	Platin 100%	19	8	NA	NA
Nowak [25]	Sunitinib	II	Pleura (100%)	E (70%) S (2%) B (17%) NA (11%)	Platin/Pem (79%) Platin/Gem (21%)	53	10	NA	6,7
Drugs targeting EGFR									
Govindan [28]	Gefitinib	II	Pleura (98%) Periton (2%)	E (79%) S (7%) B (12%) NA (2%)	None	43	4	2.6	6.8
Anderson [29]	Gefitinib	II	Pleura (100%)	NA	None	20	5	NA	14.1
Garland [30]	Erlotinib	II	Pleura (100%)	E (44%), S (3%),	None	63	0	2	10

Table 1 continued

Author	Agent	Phase	Primary tumor	Histology	Previous systemic treatments	No. of pts.	Res. (%)	mPFS (months)	mOS (months)
				B (11%), NA (41%)					
Drugs targeting VEGFR									
Jahan [40]	Vatalanib	II	Pleura (87%) Periton (6%) Other 6%	E (80%), S (11%), B (9%)	None	46	11	4.1	10
Garland [44]	Cediranib	II	NA	NA	Platin (100%)	45	9	3[b]	10[b]
Kindler [46]	Semaxanib	II	NA	NA	N/A	9	11	NA	12.4

B biphasic, *Carbo* carboplatin, *Cis* cisplatin, *E* epithelial, *Gem* gemcitabine, *mOS* median overall survival, *mPFS* median progression-free survival, *Pem* pemetrexed, *RES* response, *S* sarcomatoid, *Thal* thalidomide, Vnb vinorelbine

[a] Neoadjuvant

[b] Estimated results. Final results are N/A

adverse prognostic factor, occurring in many patients with MM [7]. Indeed high serum PDGF in MPM patients seems to be an independent predictor of poor survival [8]. Overexpression of PDGF-alpha has been shown in MM cell lines, and blocking of the PDGFR has led to growth inhibition in vitro [3]. This combined with the fact that expression of c-Kit is seen in 26% [9] of MM patients spurred clinical trials investigating imatinib in MM. Imatinib is a selective tyrosine kinase inhibitor (TKI) of the bcr/abl-mutated tyrosine kinase as well as c-kit and the PDGFR. Four phase II clinical trials of imatinib as a single agent in MM have been published. A total of 94 patients were included in these four trials without responders [10–13]. A trial by Mathy et al. included 25 patients reported a median OS of a whole 398 days. For 3 patients, there was a stabilization of disease (SD) for longer than 6 months [11]. Porta et al. treated 11 MPM patients. The trial included chemotherapy naïve as well as pretreated patients. No responders were seen but 4 (36.4%) patients obtained SD. The remaining 7 (63.6%) patients had progression of disease (PD). OS was 20 week with a fairly better survival in patients with SD (29.5 vs. 14 weeks) [12]. In a trial by Millward et al., 29 MPM patients were included. Best response was SD in 11 patients of which 4 patients had SD in more than 4 months and 1 patient had reduction in pleural thickness by 25% [10]. These results have not warranted further studies of imatinib as a single agent in MM. In vitro and in vivo experiments have indicated that imatinib may enhance the chemotherapy sensitivity to gemcitabine and pemetrexed in MPM [14]. PDGFR is a mediator of interstitial fluid pressure (IFP). Thus, the inhibition of PDGFR with imatinib with paclitaxel has been shown to lower the IFP with a possible subsequent improvement in drug delivery and increased efficacy in vitro [15]. One phase I trial with imatinib in combination with gemcitabine included 5 patients with MM. One patient had partial response (PR) [16]. A phase I trial was investigating imatinib in combination with pemetrexed and cisplatin [17]. Similarly, a phase II trial evaluating imatinib in combination with gemcitabine is being planned. Primary end point will be overall RR, and secondary end points will be PFS, OS and safety [18].

Dasatinib is an inhibitor of the Src family of non-receptor tyrosine kinases and PDGFR. Preclinical trials have shown that dasatinib has cytotoxic effects and leads to decreased migration and invasion in mesothelima cell lines [19]. A trial by Tsao et al. used dasatanib as neo-adjuvant treatment in operable MPM patients. Primary end point was evaluation of Src (Tyr419) as a predictive biomarker. Fifteen enrolled patients received 4 weeks of preoperative dasatinib treatment followed by pleurectomy/decortication (P/D) in 10 patients and extrapleural pneumonectomy (EPP) in 5 patients. Responding patients

received 2 years of dasatinib maintenance after postoperative adjuvant radiotherapy and chemotherapy were given. Preliminary data showed that 1 out of 15 enrolled patients had minor response and 12 patients had PD after 4 weeks of treatment [20]. Another phase II trial was conducted in 46 inoperable patients with no responders and PFS and median OS of 2.0 months and 4.8 months, respectively [21]. Currently, an ongoing phase II study evaluates dasatinib in previously treated MM patients [22].

Sorafenib is an inhibitor of VEGFR-2 and PDGFR-beta. Two phase II trials including a total of 70 MM patients showed modest RR of 4% and 8% [23, 24]. A trial by Janne et al. including 51 patients included both chemotherapy naïve patients and patients previously treated with chemotherapy. SD was seen in 28 (60%) patients, and median OS was 10.7 months. PFS was 3.7 months and 3-month PFS was 78%. The PFS were 3.6 and 3.6 months, and the median OS were 4.9 months and 14.6 months in chemo naïve and previously treated patients, respectively. The improved clinical outcome in previously treated patients most likely reflects patient selection [24]. In the trial by Irshad et al., 19 MM patients were included. The study, which is still ongoing, also evaluates changes in FDG-PET activity as a measure of response. One PR was observed and 13 patients obtained SD as best result, of which 5 (31%) remained progression free at 24 weeks [23].

Sunitinib is a multi-targeted TKI that blocks the tyrosine kinase activities of VEGFR-2, PDGFR-beta, and c-Kit. One trial by Nowak et al. reported preliminary data of sunitinib in MPM as second-line treatment after first-line treatment with platinum and antimetabolite (pemetrexed/gemcitabine). Primary end point is safety and efficacy. Modified RECIST criteria or metabolic response on FDG-PET in patients without prior talc pleurodesis is used for response evaluation. The RR was 10% and median OS was 6.7 months among the 53 enrolled MPM patients. SD was seen in 33 (66%) patients [25].

Epithelial growth factor receptor (EGFR) (Table 1)

The epithelial growth factor receptor (EGFR) plays a role in cell proliferation, differentiation, migration, adhesion, and survival [26]. Tyrosine kinase EGFR is overexpressed at both protein and transcriptional level in more than 50% of MPM patients [27]. Overexpression of EGRF seems to predict favorable prognosis probably because of greater EGRF expression in the epitheliod cell type compared with the sarcomatoid cell type [26].

Two phase II trials in first-line treatment with the EGFR TKI gefitinib in MPM have been conducted. Among 63 patients included in the two clinical trials, 2 PR and 1 complete response (CR) were seen [28, 29] (Table 1). The trial by Lee et al. included 21 MPM patients. PR was seen in 1 patient, and SD was seen in 10 (50%) patients. The reported median OS of 14.1 months likely reflect patient selection and possibly the effect of chemotherapy as salvage therapy [29]. Govindan et al. included 43 chemotherapy naïve MM patients. Ninety-seven percentage of the enrolled patients had EGFR overexpression. One CR and one PR were seen. Both responders had epitheloid subtype and CALGB prognostic group of three. Twenty-one (49%) patients had stable disease up to 24 weeks. Median PFS was 2.6 months, and only 40% of patients remained progression free for at least 3 months. There were no difference in PFS when comparing patients with low EGFR and high EGFR expression. Patients with high EGFR-expressing tumors had median OS of 8.1 months, while patients with low EGFR-expressing tumors had median OS of 3.6 months. Median OS of all patients was 6.8 months. Similarly, patients with epitheloid tumor histology had median OS of 7.7 months while patients with non-epitheloid histology had median OS of 2.9 months. No difference in PFS was seen regarding histological subtype [28].

Erlotinib is another EGFR TKI. One phase II trial by Garland et al. investigated erlotinib in previously untreated MPM patients included 63 patients. No objective responses were seen. SD was seen in 42% of patients and lasted at least 6 weeks. The median OS was 10 months. Analysis did not find any correlation between EGFR expression and SD. Erlotinib did not show any efficacy against MPM in spite of high expression of EGFR [30] (Table 1). One trial with a combination of erlotinib and bevacizumab will be mentioned later [31] (Table 2). One reason for the low efficacy of EGFR inhibitors in spite of over expression of the receptor might be that mutations in EGFR are rare in MM [32].

VEGF/VEGFR (Tables 1, 2)

Vascular endothelial growth factor (VEGF) is an autocrine growth factor leading to angiogenesis through the binding of endothelial cell receptors. Preclinical studies have shown that VEGF and VEGFR are highly expressed in MPM. Moreover, VEGF levels in MM patients are higher than in healthy individuals or in patients with other malignancies [33]. A high level of VEGF is positively correlated with microvascular density and is associated with a poor prognosis [34], and it has been observed that VEGF levels increase with more advanced disease stages in MPM [35]. VEGF stimulates MPM cells in a dose-related manner, and the growth of MPM cell has shown to be inhibited by anti-VEGF antibodies [36].

Bevacizumab is a monoclonal antibody targeting VEGF. A phase II trial by Jackman et al. combined erlotinib and bevacizumab to obtain a dual inhibition of EGFR and VEGFR. The trial included 24 patients did not result in any

Table 2 Drugs targeting vascular endothelial growth factor in non-resectable malignant mesothelioma patients

Author	Agent	Phase	Primary tumor	Histology	Previous systemic treatments	No. of Pts.	Res. (%)	mPFS (months)	mOS (months)
Drugs targeting vascular endothelial growth factor (VEGF)									
Jackman [31]	Erlotinib + Bvz	II	Pleura (100%)	E (67%)	Platin/Pem (67%), Platin/Gem (12%), Pem/Gem (21%)	24	0	2.2	5.8
				S (8%)					
				B (25%)					
Karrison [37]	Gem + Cis + Bvz versus gem + Cis	II	Pleura (93%/91%)	E (74%/67%)	None	115	25/22	6.9/6.0 ($P = 0.88$)	15.6/14.7 ($P = 0.91$)
Zalcman [39]	Pem + Cis + Bvz versus Pem + Cis	II/III	Pleura (100%)	E (81%)	None	111	[a]	NA	NA
				Other (19%)					
Dowell [38]	Pem + Cis + Bvz	II	Pleura (85%)	E (62%)	None	45	41[b]	6.9	15.3
			Periton (12%)	S (15%)					
			Tvag (3%)	B (20%)					
				NA (2%)					
Pavlakis [49][c]	Thal + Cis/Gem	II	NA	NA	None	31	14	NA	11
Pavlakis [49][c]	Thal	II	NA	NA	NA	27	6	NA	11
Baas [48]	Thal	I	Pleura (100%)	E (90%), Other (10)	Prior chemo (33%)	40	NA	NA	7.6

B biphasic, *Bvz* bevacizumab, *Cis* cisplatin, *E* epithelial, *Gem* gemcitabine, *mOS* median overall survival, *mPFS* median progression free survival, *Pem* pemetrexed, *RES* response, *S* sarcomatoid, *Thal* thalidomide, *Tvag Tunica vaginalis*

[a] RR = 14.4% versus N/A (25/34 patients (73.5%) with disease control (1 CR, 15 PR, 9 stable disease) in bevacizumab arm versus 16/37 (43.2%) with disease control in non-bevacizumab arm ($P = 0.010$))

[b] Preliminary data presented at ASCO 2009—final results are N/A

[c] 2 Parallel studies

responders. Twelve patients (50%) had SD for at least 2 cycles. The median PFS was 2.2 months and median OS 5.8 months. Eight patients required dose reduction, and 2 patients discontinued treatment due to toxicities, e.g., rash, diarrhea, and dysphagia [31] (Table 2).

Another randomized phase II trial by Kindler et al. compared cisplatin and gemcitabine with or without bevacizumab. One hundred and fifteen inoperable chemotherapy naïve patients were included. The treatment was well tolerated but no improved clinical benefit was observed in the bevacizumab arm. Response rates were 25% and 22%, and median OS were 15.6 and14.7 months, respectively. A subset analysis suggested longer survival in patients with low circulating levels of VEGF [37].

Radaideh et al. combined treatment with cisplatin and pemetrexed with that of bevacizumab in a phase II trial. The trial included 45 inoperable chemotherapy naïve MM patients. Primary end point the presented subanalysis was association between hypertension and clinical outcome. Preliminary results revealed a response rate of 41%, median PFS of 6.9 months, and median OS 15.3 months. Development of hypertension was reported as a possible surrogate marker for bevacizumab activity and was a significant predictor of outcome [38].

A two-armed phase II/III trial by Zalcman et al. compared an often used treatment with cisplatin and pemetrexed with or without bevacizumab as first-line treatment in inoperable MPM patients. A preliminary analysis of the study revealed that the response rate in the cisplatin-pemetrexed-bevacizumab arm was mere 14.4%. Patients with disease control (CR + PR + SD) at 6 months were statistically significant at 73.5% and 43.2% ($P = 0.010$), respectively, in favor of the bevacizumab arm. The treatment was well tolerated [39] (Table 2).

Vatalanib is an inhibitor of all VEGFRs. One phase II trial by Jahan et al. evaluated valatanib in previously untreated patients. The trial did not achieve the protocol-specified 3-month PFS of 75%, but it yielded a RR of 11% and a PFS of 4.1 months. Median OS was 10 months. There was no correlation between baseline VEGF or PDGF levels and response, PFS, or survival [40] (Table 1).

Cediranib is a potent pan-VEGFR inhibitor that has antitumor activity in several solid tumors [41–43]. One phase II trial by Garland et al. included 54 patients with MPM who had received prior treatment with platinum-based chemotherapy. Preliminary results showed a PR in 9% of patients, median PFS of 2 months, and median OS of 10 months. Fifteen patients (33%) had SD [44] (Table 1). This trial has led to the initiation of a combined phase I and randomized phase II trial comparing cisplatin and pemetrexed with or without cediranib in chemotherapy naïve MPM patients. Primary outcomes are the maximal tolerated dose of cediranib and safety/toxicity and PFS [45].

Semaxanib is an inhibitor of the VEGF-1 receptor and, less potently, PDGFR and c-Kit. One phase II trial included 9 pretreated patients resulted in PR in 1 patient [46]. Semaxanib is no longer produced after reports of severe side effects, e.g., excessive risk of thrombosis. Moreover, as the oral bioavailability of semaxanib is low, it requires intravenous administration [47] (Table 1).

Thalidomide inhibits angiogenesis through inhibition of VEGF, basic fibroblast growth factor, and tumor growth factor-alpha (TGF-alpha). A phase I trial by Baas et al. was conducted with thalidomide in 40 MPM patients with 33% of patients being chemotherapy naïve. There were no responders, and OS was 7.6 months. Eleven (27.5%) were free of progression after 6 months [48]. Two parallel phase II studies by Pavlakis et al. evaluated thalidomide in combination with gemcitabine/cisplatin or thalidomide as a single agent. Twenty-seven patients who had received prior chemotherapy or were unsuitable for chemotherapy were treated with single agent thalidomide. Responses occurred in 6% of the patients, and OS was 11 months. Thirty-one chemotherapy naïve patients received thalidomide and gemcitabine/cisplatin in another trial. Partial responses occurred in 14%, and OS was 11 months [49] (Table 2). The currently ongoing NVALT phase III trial includes patients who have not progressed after first-line treatment. Patients must have received 4–6 cycles of pemetrexed with or without platinum and are randomized to receive either no treatment or thalidomide 100 mg nightly increasing to 200 after 2 weeks. Treatment with thalidomide will continue up to 1 year. The main objective is whether the treatment with thalidomide will lead to increased PFS [34, 50].

PI3K/AKT/mTOR pathway (Table 3)

Rapamycin (sirolimus) is a natural macrolide, produced by streptomyces hygroscopicus, which has antifungal and immunosuppressant activities. Sirolimus is approved as an immunosuppressant used especially in kidney transplants. Sirolimus has an antiproliferative effect on the PI3K/AKT/mTOR pathway through the tyrosine kinase mTOR (mammalian target of rapamycin). The PI3K and AKT are often hyperactivated in human cancers and lead to cancer cell growth and invasiveness. The PI3K/AKT/mTOR pathway is often aberrant in MPM, and in vitro studies have shown that inhibition of the pathway may induce apoptosis in MPM cell lines [51, 52]. The derivate of rapamycin—temsirolimus–has been evaluated in a phase I trial including 2 MM patients. None responded to the treatment [53]. One in vitro study showed synergistic antitumor effect against MPM cell lines of a combination of cisplatin and sirolimus [54]. One in vitro study indicates that sirolomus and cisplatin in combination increases the

Table 3 Miscellaneous targeted treatments for non-resectable malignant mesothelioma patients

Author	Agent	Phase	Primary tumor	Histology	Previous systemic treatments	No. of pts	RES (%)	mPFS (months)	mOS (months)
Drugs targeting mesothelin									
Laheru [62]	MORab-009	I	NA	NA	NA	13	0	NA	NA
Hassan [61]	MORab-009	I	Pleura (50%) Periton (50%)	E (100%)	NA	8	0	NA	NA
Drugs targeting PI3K/AKT/mTOR pathway									
Raymond [53]	Temsirolimus	I	NA	NA	NA	2	0	NA	NA
Drugs targeting RNA									
Stanislaw [64]	Ranpirnase	II	NA	E (47.6%) Other (15.2%) NA (37.2%)	Prior chemo (37.1%)	105	4.9	3.4	6
Reck [65][a]	Ranpirnase + Doxo versus doxo	III	NA	NA	Pem (54%) Other (46%)	413	NA	NA	11.1 versus 10.7
Tumor necrosis factor									
Gregorc [69]	NGR-hTNF	II	NA	E (79%), Other (21)	Platin/Pem (93%) Gem/Cis (7%)	57	2	2.8	12.1
Histone deacetylate inhibitors (HDACi)									
Kelly [73]	SAHA (Vorinostat)	I	NA	E (70%) B (23%) NA (7%)	Prior chemo (92%)	13	0	NA	NA
Scherpeereel [77]	Valproic acid + doxo	II	Pleura (100%)	E (80%) NA (20%)	Prior chemo (100%)	45	16	2.5	6.7
Ramalingam [74]	SAHA (Vorinostat)	I	Pleura (100%)	NA	NA	1	0	NA	NA
Ramalingam [76]	PXD101 (Belinostat)	II	Pleura (100%)	E (54%), S (8%) NA (38%)	Cis/Pem (60%) Carbo/Pem (32%) Cis/Gem (8%)	13	0	1	5

B biphasic, *Cis* cisplatin, *Doxo* doxorubicine, *E* epithelial, *Gem* gemcitabine, *NGRhTNF* asparagine–glycine–arginine–human tumor necrosis factor alpha, *Pem* pemetrexed, *S* sarcomatoid

[a] In a preplanned analysis including 130 pretreated patients a significant advantage in survival in favor of DOX + ranpirnase was found (MST: 10.5 vs. 9 ms; HR 1.49, 95% CI 1.02–2.17)

cytotoxic effect compared with either drug alone [54]. Everolimus (RAD001) is an orally administered mTOR inhibitor and is currently being evaluated in 2 phase II trials planned to enroll 39 and 55 pretreated patients, respectively [55, 56].

Mesothelin (Table 3)

MORAB-009 is monoclonal antibody targeting mesothelin. Mesothelin is highly expressed in several cancers, including MM, ovarian cancer, pancreatic cancer, and some squamous cell carcinomas. Mesothelin is highly expressed in almost all MM of the epithelioid subtype, but not in the sarcomatoid or in the epithelial cells of the biphasic subtype [57–59]. The high membrane expression of mesothelin in MM and the limited distribution of mesothelin in normal tissues raised interest for mesothelin as an antitumor target [60]. Two phase I trials have been conducted including 23 patients. No responders were encountered among MM patients [61, 62]. Currently, an open label trial is being conducted treating MPM patients with MORAB-009 in combination with pemetrexed and cisplatin. Primary end points are efficacy and safety [63].

Ribonuclease (Table 3)

Ranpirnase is a ribonuclease that breaks down RNA. This irreparable RNA damage may constitute a death signal for apoptosis and also contribute the inhibition of the cell growth and proliferation. Ranpirnase has been tested in one phase II trial with 105 mesothelioma patients with 67% being chemotherapy naïve. RR was 4.9% and OS 6 months; 15.2% of patients were removed from the study due to adverse effects, e.g., renal insufficiency, allergic reaction, arthalgia and peripheral edema [64]. A phase III trial compared ranpirnase plus doxorubicine and single agent doxorubicine. Ranpirnase plus doxorubicin did not improve OS. A preplanned analysis including 130 pretreated patients showed significant survival advantage in favor of ranpirnase plus doxorubicin with mean survivals of 10.5 versus 9.0 months, respectively [65].

Asparagine–glycine–arginine–human tumor necrosis factor-alpha (NGR-hTNF) (Table 3)

Tumor necrosis factor-alpha (TNF-alpha) has antitumor activity through activation of apoptosis. However, treatment with NGR-hTNF has severe toxicities, which only allow tumor necrosis factor to be administered in doses that are at least tenfold lower than the effective dose in preclinical models [66–68]. NGR-hTNF consists of human TNF-alpha fused to the tumor-homing peptide asparagine–glycine–arginine (NGR) able to selectively bind an aminopeptidase N-isoform overexpressed on tumor blood vessels. A phase II trial by Gregorc included 57 patients evaluating NGR-hTNF. PR was seen in one (2%) patient. Eighteen (31%) patients with SD had a median PFS of 4.4 months. Overall, PFS and OS were 2.8 months and 12.1 months, respectively. The treatment was well tolerated [69]. This led to the initiation of a pivotal randomized double-blinded phase III trial expected to enroll 400 MPM patients. Patients who are pretreated with pemetrexed and candidate to either supportive care alone or chemotherapy are randomized to NGR-hTNF plus best investigators choice (BIC) versus placebo. BIC includes either supportive care or gemcitabine or vinorelbine [70].

Histone deacetylase inhibitors (HDACi) (Table 3)

Histone proteins exist in either acetylated or deacetylated configurations, and the equilibrium between the two forms is regulated by histone acetyltransferase and histone deacetylase (HDAC). When deacetylated, the histones bind to DNA, which are thereby rendered transcriptionally inactive. Through this mechanism, HDACi are very potent inducers of apoptosis [71]. Suberoylanilide hydroxamic acid (SAHA/vorinostat) has already shown activity in the treatment of cutaneus T-cell lymphoma [72].

In 2005, the first phase I trial concerning vorinostat in patients with MPM was published by Kelly et al. [73]. Out of 73 patients enrolled, 13 patients had MPM. Only one MM patient was chemotherapy naïve. In 2 patients (15%), initial radiographic response was seen, but this was later unconfirmed. Four patients (30%) had SD. Dose limiting toxicities were anorexia, dehydration, diarrhea, and fatigue. A phase I trial by Ramalingham et al. combined vorinostat with carboplatin and paclitaxel led to SD in the one included MPM patient [74]. These results have led to the initiation of a phase III trial planned to include 660 MPM patients who have progressed after treatment with pemetrexed and platinum. Patients are randomized 1:1 to receive vorinostat 300 mg two times a day or placebo. Primary outcome will be OS and number of patients with grade 3/4 adverse effects [75].

Ramalingham et al. evaluated another HDACi, Belinostat, in a phase II trial in 13 patients. There were no responders, and PFS was only 1 month and OS was 5 months. Only two patients (15%) had SD [76]. In vitro studies suggest increased efficacy of HDACi in combination with other agents [71].

In vitro data suggest that valproic acid has proapoptotic effect, which was synergized with doxorubicine. This led to a phase II trial by Scherpeereel et al. that included 45 pretreated patients to treatment with valproic acid in combination with doxorubicine [77]. PR was seen in 7 patients (16%), all with good initial performance status.

Best disease control rate (PR + SD) was 36% (CI 22–51%). Median response duration was 11.8 months. Median PFS and median OS were 2.5 months and 6.7 months, respectively.

Newer drugs and targets under investigation

Most cancer cells are dependent on the G2 checkpoint to survive this has led to the development of CBP501, which is a G2 checkpoint abrogator. One phase 1 trial by Geoffrey et al. included 3 patients, which were treated with CGP501 in combination with cisplatin [78]. One patient had PR and PFS of 9.7 months. Two patients had SD that lasted for 11 months and 3 months, respectively. A combined phase I/II trial is currently ongoing enrolling patients with solid tumors (phase I) and MPM patients (phase II). Patients will receive treatment with CBP501 in combination with pemetrexed and cispatin. MPM patients will be randomized to pemetrexed and cisplatin with or without CBP501.

IMC-A12 is an antibody targeting the insulin-like growth factor 1 (IGF-1). Inhibition of IGF-1 receptor has lead to decreased cell proliferation and enhanced the cytotoxic effect of cisplatin in vitro [79]. A phase II study evaluating IMC-A12 in MM is ongoing. It is planned to enroll 55 pretreated MM patients.

Pazopanib is an oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-Kit. An ongoing phase II study is evaluating single agent pazopanib in MPM patients [80]. Similarly, axitinib is a pan-VEGFR inhibitor also inhibiting PDGFR and c-Kit. Axitinib is currently being evaluated in a randomized combined phase I/II trial where patients will be randomized to cisplatin and pemetrexed with or without axitinib [81].

Bortezomib is a potent inhibitor of the 20S proteasome, which has shown to have cytotoxic effect in vitro and in MM xenografts in vivo. [82] This has led to the initiation of a phase II trial planned to enroll 111 patients to receive treatment with single agent bortezomib [83]. Bortezomib has been shown to increase the cytotoxic effect of cisplatin and pemetrexed when dosed prior to in either MPM cell lines [84]. A phase II trial evaluating bortezomib in combination with cisplatin as first-line treatment in MM patients is currently ongoing. Primary end point is PFS at 18 weeks. The trial are planned to enroll 76 patients. Patients will receive up to 6–3-week cycles of cisplatin and bortezomib in the absence of PD or unacceptable toxicity [85].

Cetuximab, an antibody-targeting EGFR, is currently being evaluated in combination with cisplatin/carboplatin and pemetrexed as first-line treatment in MPM patients. Patients will be treated with standard chemotherapy (4–6 cycles), combined with weekly administration of cetuximab until disease progression. The trial is planned to enroll 18 MPM patients [86].

Azatidine is a cytidine analog, which is currently being tested in a phase I study in combination with thalidomide in patients with either soft tissue sarcoma or MM [87].

Discussion

The prognosis of MM is still poor, and there is a need for more effective antineoplastic drugs. The better understanding of the biology of MPM has led to the assessment of a number of targeted agents. Targeted treatments have been explored in several other cancer types and might be beneficial in the treatment of some, e.g., bevacizumab in non-small cell lung cancer (NSCLC) [88, 89] and in other malignancies such as breast cancer, glioblastoma, colon cancer, and ovarian cancer [90–93]. Another example is gefitinib in chemotherapy naïve NSCLC patients harboring EGFR mutations [94].

There are several challenges concerning clinical trials of targeted malignant mesothelioma, which is reflected in the somewhat suboptimal design in some clinical designs described in this review. The double-blinded randomized clinical trial remains the 'gold standard' of clinical trial design, but is hampered by the relative rarity of this disease. Of importance, the clinical trials are clear definition of the study populations, end points, sample sizes, power calculations, treatment allocations, and stratifications [95].

The accrual and stratification of mesothelioma patients may cause potential problems especially in first-line experimental treatments due to the fact that chemotherapy naïve MM patients are currently usually receiving platinum-based doublet chemotherapy often with pemetrexed. Hence, most chemotherapy naïve MM patients included in recent clinical trials with targeted treatment have not been fit to receive such standard chemotherapy. A trial including mainly patients with poor performance status may negatively influence the outcome observed in the clinical trials with targeted agents in first-line treatment.

It is also important to include enough patients to make firm conclusions on efficacy. The sample size obviously depends on the end point selected and also the expected grade of difference between treatment arms. Stratification based on biomarker status could be considered. Populations harboring specific biomarkers may make it possible to reduce the needed sample size, but it will not be possible to generalize the results due to lack of reliable biomarkers and unknown off-target effects.

Stratification based on biomarkers has been successful in the case of imatinib in the treatment of chronic myeloid leukemia and gastrointestinal stromal tumors (GIST). CML often harbors activating mutations in BCR-ABL, and GIST often has activating mutations in c-Kit [96]. Imatinib entered clinical trials in mesothelioma due to the effect on

c-Kit, which is expressed in about 26% of MM patients [9]. However, expression of unmutated c-kit in MM may not predict efficacy of imatinib [97]. Stratification based on biomarker status in future MM trials seems warranted.

Phase II trials are most commonly used to evaluate antitumor efficacy using objective response as the surrogate end point for patient benefit, but it is not possible to directly translate response to an improved PFS or OS, which especially gives rise to difficulties when evaluating targeted drugs for which SD is the main criterion of efficacy. Also, it is challenging to compare objective response between different clinical trials due to the fact that response evaluation is inherently difficult in MPM because of the growth along the pleural surface causing problems when measuring the longest uni-dimensional diameter of the target mass. To solve this problem, Nowak et al. suggested modified RECIST criteria measuring tumor size perpendicular to the thoracic wall or mediastinum instead of longest diameter to produce more accurate and objective response evaluations [98]. However, a notably interobserver variability is still observed. Another solution could be the use of PET-CT, which is a promising evaluation modality in all stages of MPM including evaluation of treatment response [99] but it still needs further evaluation.

OS is another common end point, which is defined as the time from randomization to the time of death [100]. OS is an accurate endpoint, which can be evaluated easily and precisely, and evaluation of OS is not subject to predetermined intervals. Furthermore, the evaluation of OS includes the entire intention to treat population instead of only evaluating subset groups. Although OS is a precise end point, it is influenced by patient and tumor characteristics, comorbidity and stage, thus hampering comparison between trials. Another obstacle when comparing OS is the number and types of previous and subsequent treatments after progression. Especially with newer and more efficient drugs, OS may require longer follow up periods, which leads to the risk of patients being lost to follow-up. Furthermore, to reveal significant difference in OS between treatment arms, large patient populations are required.

PFS is the duration of time from randomization to tumor progression or death of any cause. PFS is thus not sensitive to subsequent drug treatment as the progression event has already occurred before initiation of subsequent treatment. The events occurs earlier when using PFS than OS making it possible to collect and analyze PFS data earlier, and also, fewer patients may be required to show a statistical difference between treatment arms [101]. PFS seeming a suitable end point for evaluating targeted drugs. Another alternative is PFS rate at 3, 4, 5, or 6 months, which are easily obtainable endpoints, as the event is a rate at predefined time [102].

The design problems of phase II trials give rise to challenges when evaluating whether a potential drug candidate should proceed to a randomized phase III trial while phase III trials make it is possible to evaluate OS benefit or improvements in PFS ,they are also expensive and may carry ethical problems if the preceding phase II trial has not shown promising efficacy of the drug. In some cases, it may be possible to go directly from phase I testing to phase III testing whether the drug has shown great potential in the phase I setting as seen in the case of vorinostat.

Drugs explored in first-line treatment include the tyrosine kinase inhibitors dasatanib, vatalanib, gefitinib, and erlotinib that have all been explored in chemotherapy naïve MM patients. None showed RR exceeding 12% or PFS above 4.1 months. Median OS varies widely from 5.0 to 13.1 months. Gefitinib was used in two first-line trials with low RR of 4% and 5% and median OS of 6.8 and 14.1 months, respectively [20, 27, 30, 103]. Despite low RR and short PFS, some studies present median OS above 10 months, which compares with current first-line chemotherapy of MPM [4]. The trials exploring TKI are all phase II trials with limited number of patients, and activity of these drugs is not firmly established. In contrast, the addition of the VEGFR inhibitor bevacizumab to chemotherapy with pemetrexed and cisplatin in a randomized phase II/III trial was significantly superior to the same chemotherapy without bevacizumab with regard to response and disease stabilization [39]. A similar randomized phase II trial did not find significant clinical benefit of the addition of bevacizumab to gemcitabine and cisplatin [37]. Addition of bevacizumab to standard treatment for MM merits further evaluation.

Drugs explored in second line and above include Sorafenib, imatinib and cediranib, which have all been, explored both in trials that included both chemotherapy naïve patients and in previously treated patients. None showed RR higher than 9% or PFS longer than 3.7 months in second line or above. As for OS, there were wide variations. Imatinib in combination with gemcitabine also failed to produce responders. Bevacizumab in combination with erlotinib did not produce any responders but OS was 5.8 months. Second-line thalidomide yielded OS of 11 months, which may merit further examination. Overall, targeted treatments alone in second-line treatment of MM does not currently induce better clinical outcomes than hitherto-reported chemotherapy regimens, which revealed RR of 5.5–32.5%, PFS of 2.2–7.4 months, and OS of 4.1–10.9 months [6]. Several trials report stabilization of disease in a number of patients. Coupled with the fact that several of the targeted drugs in vitro seem to enhance the cytotoxic effect of classic chemotherapy, targeted drugs may theoretically provide clinical benefit in combination therapies which should be explored. Furthermore, the efficacy seen in some patients might represent undefined

subgroups that will benefit from treatment. Search for predictive markers to define potential subgroups should be urged as targeted treatment may likely be inefficient when treating unselected groups of patients. Research in tumor biology continues to discover promising targets, which could be explored in MM, e.g., the EML4-ALK inhibitor, crizotinib that produced very promising results in the treatment of NSCLC pending activating mutations [104]. It remains unknown whether the histological subtype of MM or expression of tumor markers exhibits is important when selecting targeted treatments, though a trial by Govindan et al. evaluating gefitinib suggested an improved OS for a subgroup having high EGFR expression and epitheloid subtype [28]. It may also be speculated that some targeted drugs may be efficient when combined with conventional chemotherapy, such as in the case of bevacizumab. Targeted agents like gefitinib, erlotinib, bevacizumab, and in the future probably also crizotinib are currently used in the treatment of NSCLC but it seems that MM has different genetic properties as these agents are not similarly active in MM compared with NSCLC, e.g., EGFR mutations are rare in MM compared with NSCLC. Separate trials of potential biomarkers should be conducted in MM to further explore this field, which is necessary to improve clinical results in the future.

Conflicts of interest None.

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