



Investigational approaches for mesothelioma

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Malignant pleural mesothelioma (MPM) is a rare, aggressive tumor with a poor prognosis. In view of the poor survival benefit from first-line chemotherapy and the lack of subsequent effective treatment options, there is a strong need for the development of more effective treatment approaches for patients with MPM. This review will provide a comprehensive state of the art of new investigational approaches for mesothelioma. In an introductory section, the etiology, epidemiology, natural history, and standard of care treatment for MPM will be discussed. This review provides an update of the major clinical trials that impact mesothelioma treatment, discuss the impact of novel therapeutics, and provide perspective on where the clinical research in mesothelioma is moving. The evidence was collected by a systematic analysis of the literature (2000–2011) using the databases Medline (National Library of Medicine, USA), Embase (Elsevier, Netherlands), Cochrane Library (Great Britain), National Guideline Clearinghouse (USA), HTA Database (International Network of Agencies for Health Technology Assessment – INAHTA), NIH database (USA), International Pleural Mesothelioma Program – WHOLIS (WHO Database), with the following keywords and filters: mesothelioma, guidelines, treatment, surgery, chemotherapy, radiotherapy, review, investigational, drugs. Currently different targeted therapies and biologicals are under investigation for MPM. It is important that the molecular biologic research should first focus on mesothelioma-specific pathways and biomarkers in order to have more effective treatment options for this disease. The use of array technology will be certainly an implicit gain in the identification of new potential prognostic or biomarkers or important pathways in the MPM pathogenesis. Probably a central mesothelioma virtual tissue bank may contribute to the ultimate goal to identify druggable targets and to develop personalized treatment for the MPM patients.

Keywords: mesothelioma, chemotherapy, targeted therapy

INTRODUCTION

The etiology, epidemiology, diagnosis, prognosis, and management of MPM have recently been reviewed and guidelines have been issued (Stahel et al., 2009; Scherpereel et al., 2010). Malignant pleural mesothelioma (MPM) is a rare but aggressive neoplasm that arises from the mesothelial surfaces of the pleural cavity. MPM has a bad prognosis: median survival of untreated cases is 6–9 months with less than 5% 5-year survivors. Essential prognostic factors associated with better outcome are earlier stage and epithelioid histologic type (UICC, 2006). Additional prognostic factors are the presence of symptoms, performance status, age, gender, and weight loss. The prognostic value of asbestos exposure is controversial.

MANAGEMENT OF MPM: STANDARD OF CARE

Palliative radiotherapy

The aim of palliative radiotherapy is pain relief and may be considered in cases of painful chest wall infiltration or nodules (Ung et al., 2006). Responses of over 60% have been seen, although the duration of response – a median of 2–3 months – is often disappointing. The optimum dose has not been shown and many of the series were small and retrospective. Palliative radiotherapy is more effective if bone erosion or subcutaneous masses are present and less for diffuse pain, dyspnoea, superior vena cava syndrome or for retreatment.

Palliative surgery

Debulking pleurectomy/decortication (P/D) can be defined as significant but incomplete macroscopic clearance of pleural tumor. The objective of the operation is to relieve an entrapped lung by removing the visceral tumor cortex. Removal of the parietal tumor cortex may relieve a restrictive ventilatory deficit and reduce chest wall pain. The operative procedure needs to be further standardized and may be performed by either open thoracotomy, but the closed video assisted thoracoscopic surgery (VATS) is preferred. There are series of retrospective studies which provide low grade evidence for P/D (Waller et al., 1995; Soysal et al., 1997; Martin-Ucar et al., 2001; Halstead et al., 2005; Muirhead and O'Rourke, 2007; Nakas et al., 2008).

Palliative chemotherapy

Two international randomized studies (Vogelzang et al., 2003; Van Meerbeeck et al., 2005) suggested that combination chemotherapy including cisplatin and an antifolate, either pemetrexed or raltitrexed, increases survival compared to single agent cisplatin. The median survival observed in both studies showed an improvement of 2.6–2.8 months for the combination arm. Based on these two randomized phase III trials, it is now generally accepted to treat patients with MPM with a combination of an antifolate with

platinum. Other cisplatin-based combinations have also produced interesting response rates of 20–30% in phase II studies: etoposide, epirubicin, gemcitabine, vinorelbine, or methotrexate (Berghmans et al., 2003; Ellis et al., 2006). The combination of carboplatin with pemetrexed shows outcome data similar to the ones obtained with cisplatin and pemetrexed (Ceresoli et al., 2008; Santoro et al., 2008). Few things we do not really know about cisplatin/pemetrexed include: when to start therapy, when to stop (maintenance?) and the role of the predictive markers TS and ERCC-1. In second line, no randomized trial has yet demonstrated any benefit in overall survival or quality of life. In the last two decades, only seven phase II studies (Harvey et al., 1984; Sorensen et al., 1985, 2007; Giaccone et al., 2002a; Porta et al., 2005; Fennell et al., 2007; Zucali et al., 2008) have addressed this question but failed to come to any recommendation. Some promising activity was noted with pemetrexed alone (Sorensen et al., 2007) and a combination of cisplatin, irinotecan, and mitomycin (Fennell et al., 2007). In a phase III study, patients with progressive disease were randomized to best supportive care (BSC) or second line pemetrexed single agent (Jassem et al., 2008). Time to progression was significantly longer in the pemetrexed arm but there was no improvement in overall survival. This might be due to significantly more patients in the BSC arm receiving post discontinuation chemotherapy with pemetrexed compared with patients randomized in the pemetrexed arm. In the case of recurrent disease it is recommended to include patients in clinical studies. Patients showing an objective and symptomatic response can be rechallenged with pemetrexed.

Radical treatment

1. *Radiation therapy* to the full hemithorax is limited by critical organs such as the lung, the liver and heart most particularly, but also the spinal cord and the esophagus. Therefore it is difficult to administer a total dose more than 54 Gy to such a large volume. Therefore, sophisticated treatment techniques, oriented by surgeon's and pathologist's findings, are needed (Maasilta, 1991; Senan, 2003). Radical radiotherapy has never been compared to chemotherapy or surgery or to BSC (as part of combination therapy) in a prospective, randomized trial and no data exist supporting one or the other treatment (Chapman et al., 2006).
2. *Radical surgery* may be defined as an attempt to remove all macroscopic tumor from the hemithorax. These objectives are usually achieved by extrapleural pneumonectomy (EPP) with an *en bloc* resection of lung, visceral and parietal pleura, and ipsilateral hemi-pericardium and hemi-diaphragm, followed by pericardial and diaphragmatic reconstruction with prosthetic material (usually Gore-Tex™). Operative mortality has fallen to an acceptable level of around 5% in experienced centers, but morbidity remains high at around 50% (Sugarbaker et al., 2004; Opitz et al., 2006). Older literature indicates that surgery alone for MPM is not curative since no oncological resection margins can be obtained. The pleural lining, especially on the pericardium and mediastinum cannot be resected with a 1 to 2-cm margin and therefore all surgical procedures are considered R1 resections (Sugarbaker, 2006) and high local recurrence rates are the rule (Baldini et al., 1997) and this observation is therefore the rationale for combined modality therapy.
3. *Postoperative radiotherapy (PORT)* with 54 Gray (Gy) to the hemithorax after EPP resulted in a local recurrence rate of 13% and a 4% local-only recurrence rate (Rusch et al., 2001). Preliminary results of intensity-modulated radiotherapy (IMRT) in the adjuvant setting after EPP seemed particularly promising as they could provide good local control and protect organs at risk such as heart or liver (Ahamed et al., 2003). However, severe pulmonary toxicity has been reported in recent studies so that it should not be recommended outside of clinical trials (Allen et al., 2006; Rice et al., 2007).
4. The only published long-term survivors among resected mesothelioma patients have undergone radical surgery (EPP) as part of a *combined modality* treatment including postoperative chemotherapy with or without PORT (Sugarbaker et al., 1999; Flores et al., 2006). The preference for neo-adjuvant chemotherapy is justified by its better compliance, lower rate of surgical morbidity, high rate of objective response, good rate of radical resections and the possibility to select the optimal patients to be submitted to surgery. This approach was explored first in a number of single institutional phase II studies with promising results (Weder et al., 2004; De Perrot et al., 2009). A number of multicentre prospective phase II trials exploring the feasibility of a multimodality approach in highly selected patients, combining neo-adjuvant chemotherapy, followed by EPP and PORT have demonstrated a similar median survival of 17–20 months (Table 1; Weder et al., 2007; Krug et al., 2009; Van Schil et al., 2010). At least 2 more multicentre phase II trials addressing the same issues are on-going.

INVESTIGATIONAL DRUG APPROACHES

NEW ANTIFOLATES, PLATINUM ANALOGS, AND NEW THIRD GENERATION CYTOTOXIC AGENTS

The cytotoxic activity of antifolates is mainly due to their ability to inhibit several different folate-dependent enzymes involved in DNA synthesis. The key enzyme in the folate metabolism of MPM is thymidylate synthase (TS). Low TS protein levels are predictive of improved overall survival in pemetrexed treated patients with MPM (Righi et al., 2010). Glycinamide ribonucleotide formyl transferase (GARFT) and dihydrofolate reductase (DHFR) might also be of importance. The most widely used antifolate in the treatment of MPM is Pemetrexed. Pemetrexed is a third generation antifolate and primarily an inhibitor of TS with also potent, but lesser, inhibition of GARFT and DHFR. It has a substrate specific high-affinity transport route in mesothelioma cell lines, favoring its use in MPM (Wang et al., 2002).

Novel antifolates include *nolatrexed*, an oral specific TS inhibitor that was developed using protein structure-based drug design, primarily for the treatment of hepatocellular carcinoma. Only one patient with MPM was included in a phase I trial and its development was halted after a negative phase III trial in hepatocellular carcinoma (Hughes et al., 1999; Gish et al., 2007). New DHFR inhibitors such as pralatrexate, talotrexin, and previtrexed have also been developed, but at the moment only pralatrexate has been tested in MPM. In a phase II study it showed no activity as a single agent (Krug et al., 2007). AG 2037 is a GARFT inhibitor being evaluated for its activity in NSCLC and colorectal cancer (Webber et al., 1996). No trials have been conducted for its effect in MPM.

Table 1 | Prospective multicentre phase II trials of radical multimodality treatment in early stage mesothelioma.

Variable	SAKK-trial (Weder et al., 2007)	US-trial (Krug et al., 2009)	EORTC trial (Van Schil et al., 2010)
N/n institutions	61/6	77/9	59/11
Induction regimen	Cis-gem × 3	Cis-pem × 4	Cis-pem × 3
Compliance to induction chemotherapy	95%	83%	93%
EPP	45 (74%)	54 (70%)	42 (74%)
Operative mortality	2.2%	7%	6.5%
PORT completed	36 (59%)	40 (52%)	37 (65%)
Median OS (ITT; range)	19.8 m	16.8 m	18.4 m
Median OS (PP)	23 m	29.1 m	NA
Local relapse (% PP)	NS	11 (28%)	6 (16%)
Median PFS (ITT)	13.5 m	10.1 m	13.9 m
Median overall treatment time (days; range)	NS	NS	184

NS, not stated; PORT, postoperative radiotherapy; ITT, intention to treat; PP, per protocol; EPP, extrapleural pneumonectomy; OS, overall survival; PFS, progression free survival.

Cisplatin and carboplatin are effective in MPM both as single agents and as a component of combination chemotherapy. The efficacy of these platinum analogs is limited by several (intrinsic and acquired) mechanisms of resistance, including impaired cellular uptake, intracellular inactivation by thiols and enhanced DNA repair. New platinum analogs have been developed to overcome this platinum resistance, though no new small molecule platinum drug has entered clinical trials since 1999. AMD 473 is a platinum analog that is less susceptible to detoxification by intracellular thiols. AMD 473 demonstrated no activity in phase II trials with a total of 41 previously treated mesothelioma patients (Giaccone et al., 2002b). Other platinum analogs including *picoplatin*, *satraplatin*, *lobaplatin*, and *nedaplatin* showed lower levels of toxicity in phase I and II trials but have failed to demonstrate superior efficacy in MPM compared to the classical platinum analogs cisplatin and carboplatin (Kelland, 2007).

Vinca alkaloids have activity in MPM. Vinorelbine is active in first and second line treatment.

In a phase II trial the efficacy and activity of a regimen of carboplatin together with vinorelbine administered i.v. and orally was evaluated. The regimen was easy to administer and generally well tolerated without any toxic deaths in spite of the poor prognostic patient population and the median survival was in excess of 9 months. The regimen was considered equally active as the combination of cisplatin and vinorelbine (Sørensen et al., 2007).

In vitro and *in vivo*, resistance to the novel vinca alkaloid *vinflunine*, develops less readily than to vinorelbine. In an phase II trial vinflunine achieved a response rate of 13.8% and a median survival of 10.8 months (Talbot et al., 2007).

Microtubule-stabilizing agents such as the taxanes have shown only modest activity in MPM. The *epothilones*, a novel class of microtubule-stabilizing agents, are being tested in breast cancer, melanoma, and renal cell carcinoma. In light of the limited effect of the taxanes, they have not been tested in MPM patients in phase II or III trials.

Amrubicin combines anthracycline activity and potent topoisomerase II inhibition.

In phase II trials of small cell lung cancer, it showed superior response rates compared to the topoisomerase I inhibitor topotecan (Jotte et al., 2010). Anthracyclines have shown activity in MPM, making amrubicin a promising future candidate for the treatment of MPM.

Trabectedin (also known as ecteinascidin 743 or ET-743) is a tetrahydroisoquinoline alkaloid isolated from a marine tunicate growing in mangrove roots. It is effective in metastatic soft tissue sarcoma. A Phase II Study is completed, but the data have not yet been published (Anonymous, n.d. f).

Alanosine (also called SDX-102) is an antimetabolite. It failed to show objective responses in a phase II trial including 16 patients with MPM (Kindler et al., 2009).

Most cancer cells are dependent on the G2 checkpoint to survive with DNA damage. The stable peptide CBP501 shows selective G2 checkpoint abrogation, with activity in various tumor models, alone and combined with DNA damaging agents. A phase I/II trial of CPB501 combined with cisplatin and pemetrexed is recruiting patients. The phase II part will evaluate full-dose cisplatin and pemetrexed combined with CBP501 (at the maximum tolerated dose, MTD determined in the phase I part) in previously untreated, unresectable MPM patients (Anonymous, n.d. e).

BIOLOGICALS AND TARGETED THERAPIES

Recent pharmaceutical developments have focused on the identification and inhibition of molecular pathways involved in the growth and progression of MPM. A number of novel agents have been or are being evaluated, including drugs targeted against the epidermal growth factor, platelet derived growth factor, vascular endothelial growth factor, src kinase, histone deacetylase, the proteasome and mesothelin (Table 2).

The epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that is over-expressed in a variety of malignancies. Signaling through EGFR is associated with inhibition of apoptosis, with resistance to chemotherapy, and metastases. EGFR was observed to be over-expressed on immunohistochemistry (IHC) in a majority of epithelioid mesothelioma specimens (Dazzi et al., 1990). Based on these data, the CALGB conducted a phase II trial that

Table 2 | Targeted agents in MPM.

Compound	Target	Stage of development	RR/MST	Toxicity	Reference
Gefitinib	EGFR	Phase II	4%/6.8 m	Diarrhea, skin, nausea	Govindan et al. (2005)
Erlotinib	EGFR	Phase II single agent	0%	Skin, nausea, diarrhea	Garland et al. (2007)
		Phase II with bevacizumab	10 m		Anonymous (2009e)
Cetuximab	EGFR	Phase II with cis/carbo and pemetrexed	–	–	Anonymous (2009b)
Imatinib	PDGFR	Phase II	0%/2–14.3 m	Edema, nausea, diarrhea	Kumar-Singh et al. (1999); Millward et al. (2003), Villano et al. (2004), Mathy et al. (2005), Porta et al. (2007)
		Phase II with gemcitabine	–	–	Anonymous (2009a)
		Phase I with cisplatin and pemetrexed	–	–	Anonymous (2009h)
Sorafenib	KDR, Flt-4, PDGFR, Raf	Phase II	4%/14.3 m	Fatigue, hand, and foot-syndrome	Janne et al. (2007)
		Phase I with doxorubicin	10.7 m		Richly et al. (2006)
		Phase II with doxorubicin			Anonymous (2009j)
Vatalanib	KDR, Flt-4, PDGFR, Raf	Phase II	11%/10 m	–	Jahan et al. (2006)
Sunitinib	Flt-1, KDR, Flt-4, PDGFR	Phase II second line	15%/5.9 m	high	Anonymous (2009m)
		Phase II first line	–	–	Nowak et al. (2008)
		Phase I platinum and pem	–	–	Anonymous (2009c)
Cediranib (AZD2171)	VEGFR, PDGFR, C-kit	Phase II	–	–	Anonymous (n.d. d)
Bevacizumab	VEGF	Phase II with cis and gem	15.6 m	Hypertension, epistaxis	Karrison et al. (2007)
		Phase II with erlotinib	–	–	Anonymous (2009e)
		Phase II with cis and pem	DCR at 6 m: 46/versus 54%; PFS 9.2 m		Zalcman et al. (2010)
Thalidomide	VEGF	Phase II	0%/SD > 6 m: 28%	7.5 m	Baas et al. (2005)
		Phase II with cis/gem	14%		Pavlakis et al. (2003)
Temsirolimus	m-TOR	Phase I	0%	–	Raymond et al. (2004)
Bortezomib	Proteasome	Phase II (second line)	–	–	Anonymous (2009g)
		Phase II with cisplatin (EORTC)	–	–	Anonymous (2009f)
Vorinostat	HDAC	Phase I	15%	nausea, vomiting	Krug et al. (2006)
		Phase III	–	–	Anonymous (2009l)
PXD101	HDAC	Phase II (second line)	–	–	Anonymous (2009i)
SS1P	Mesothelin	Phase I	12%	edema, fatigue hypoalbuminemia	Hassan et al. (2007)
		Phase II	–	–	Zhang et al. (2006)
MORAb-009	Mesothelin	Phase I	–	–	Anonymous (2009d)
CRS-207	Mesothelin	Phase I	–	–	Anonymous (n.d. j)
GC1008	TGF- β	Phase I	–	–	Anonymous (2010)
Dasatanib	Src	Phase I (resectable)	–	–	Anonymous (n.d. b)
		Phase II (pretreated)	–	–	Anonymous (n.d. a)

evaluated the role of gefitinib in the treatment of MPM (Govindan et al., 2005). No objective responses were reported and the regimen was not deemed suitable for further evaluation. Erlotinib, another EGFR inhibitor, was also evaluated in a phase II study for patients with MPM (Garland et al., 2007). No objective responses were seen despite a high rate of patients with EGFR-expressing tumors in the study. A possible explanation of absence of significant benefit from using EGFR-TKIs could be due to the absence of activating somatic mutation in EGFR-TKI domain that is strongly predictive of response to EGFR-TKIs (Cortese et al., 2006). Cetuximab, a monoclonal antibody against the EGF receptor is currently investigated in a phase II study in combination with platinum and pemetrexed (Anonymous, 2009b). Another Her-family member, ErbB-2 or Her2/neu is expressed in 97% of mesothelioma specimens on IHC. However, the ErbB-2 gene does not appear to be amplified and data from breast cancer studies suggest that specific ErbB-2 inhibitors may not be effective in the absence of amplification.

Findings derived from clinical and preclinical studies suggest that *angiogenesis* may be an important process in the pathogenesis of MPM. VEGFs and their receptors are over-expressed in MPM tissue, cell lines, pleural effusion and non-malignant mesothelial specimens and effusions (Kumar-Singh et al., 1999; Strizzi et al., 2001). Circulating VEGF and high microvasculature density significantly correlate with worse prognosis (Edwards et al., 2001). Angiogenesis allows the formation of new blood vessel essential for tumor growth. The first findings that linked mesothelioma and angiogenesis were reported by Branchaud et al. (1989). Recent data suggest the existence of relationship between SV40 and VEGF in MPM. In mesothelial cell cultures SV40 positive the levels of VEGF were significantly higher. Mesothelial cell transfected with SV40 or only with SV40 Tag antigen releases great amount of VEGF proteins and mRNA that leads to cell line proliferation. The inactivation of VEGF signal transduction pathway abolished this proliferation. Ligand–receptor interaction induces the activation of the tyrosine kinase domain of the VEGFRs, which leads to the activation of intracellular signal transduction pathways, such as the Raf/MEK/extracellular signal-regulated kinase (ERK) and the PI3K/AKT. VEGFR-1 regulates positively the angiogenesis and is thought to be important for endothelial cell migration and differentiation. VEGFR-2 mediates most downstream effects of VEGF-A, including vascular permeability, endothelial cell proliferation, invasion, migration, and survival. VEGFR-3 is involved in lymphangiogenesis, and its expression has been associated with the dissemination of tumor cells to regional lymph nodes. Proteins involved in regulating the angiogenic process have been implicated in the prognosis of MPM and can be indirectly assessed using immunohistochemistry and micro-vessel counting. Studies have indicated that increased micro-vessel density is associated with a poor outcome (Edwards et al., 2001). VEGF, the VEGF receptors (VEGFRs) flt-1 (VEGFR-1), KDR (VEGFR-2), and VEGFC and its cognate receptor VEGFR-3 have been shown to be co-expressed in MPM (Ohta et al., 1999; Strizzi et al., 2001). Both VEGF and VEGFC function as autocrine growth factors for the development of MPM.

A randomized phase II study was conducted in patients with advanced MPM to evaluate whether the addition of bevacizumab, a monoclonal antibody against VEGFR, can enhance the efficacy of chemotherapy (Karrison et al., 2007). Patients were treated

with cisplatin and gemcitabine with or without *bevacizumab*. The treatment was tolerated well without any major toxicity. Nevertheless, there was no improved outcome with the addition of bevacizumab. The median progression free survival with and without the addition of bevacizumab, were 6.9 and 6.0 months, respectively. Although the median overall survival was numerically superior for bevacizumab + chemotherapy (15.6 versus 14.7 months), this difference was not statistically significant. An exploratory subset analysis noted improved survival with bevacizumab-chemotherapy regimen in patients with low circulating levels of VEGF. The multicenter, randomized phase II-III trial (MAPS) of cisplatin–pemetrexed with or without bevacizumab showed a DCR at 6 months of 46% versus 54% for the bevacizumab arm. A promising PFS of 9.2 months was shown. Biomarker studies are on-going (Zalcman et al., 2010). Based on these results the IDMC recommended a phase III trial. An on-going phase II study is addressing the activity of bevacizumab added to erlotinib in second line (Anonymous, 2009e).

Several small molecule inhibitors of the VEGF receptor tyrosine kinase have been tested in phase II studies. The multikinase inhibitor *sorafenib* inhibits the Ras/Raf/MEK/ERK and p38 signaling pathways, VEGFR-2 and VEGFR-3, and members of the PDGF receptor family, PDGFR β and c-Kit. Sorafenib was evaluated as monotherapy for recurrent MPM in a phase II study by the CALGB (Janne et al., 2007). Treatment was tolerated well, but the response rate of 4% did not meet the criteria for further evaluation of this agent as monotherapy. In a phase I study, one patient with MPM reported a partial response when sorafenib was combined with doxorubicin (Richly et al., 2006). This combination is currently under evaluation in a phase II study in MPM (Anonymous, 2009j).

PTK 787 (*vatalanib*), an aminophenazone derivative, is an inhibitor of all known VEGFRs and, at higher concentrations, of PDGFR and c-kit. In a Phase II study, the efficacy of vatalanib was studied and correlated the response to treatment with circulating serum levels of VEGF, PDGF, and VEGF in chemo-naïve patients with MPM. RR was 11%, median OS 10 months, and PFS 4.1 months (Jahan et al., 2006). However, the study did not meet the prespecified end point of 3-month PFS rate. No correlation was observed between baseline VEGF or PDGF levels and response, PFS, or survival.

Sunitinib a tyrosine kinase inhibitor that acts on several targets, such as VEGFRs, PDGFR β , and c-Kit is under evaluation in untreated MPM patients in a phase II study (Anonymous, 2009m) and has been tested in a Phase II study on patients who failed after a platinum plus pemetrexed regimen. A partial response in 15% of patients and stable disease in 55% of them was seen. The median OS was 5.9 months and the median TTP of 3.5 months. Moreover, the role of [18 F]fluorodeoxyglucose positron emission tomography was also evaluated. A metabolic response was observed in 30% of patients without talc pleurodesis. Final results of this trial has been presented at ASCO 2010 and the authors concluded that activity was modest and toxicity high (Nowak et al., 2008). Sunitinib is under research in a phase I study in association with pemetrexed/cisplatin and pemetrexed/carboplatin and pemetrexed (Anonymous, 2009c).

Other VEGF tyrosine kinase inhibitors that are currently under evaluation include cediranib and pazopanib. AZD2171 (*cediranib maleate*), an indole–ether quinazoline derivative that acts with all three VEGFRs, with PDGFR and c-kit, is being evaluated in a Phase II study (Anonymous, n.d. d).

Thalidomide, a broadly targeted agent, inhibits angiogenesis mediated by VEGF, basic fibroblast growth factor (FGF) and TGF- α . A Phase II study evaluated the efficacy of thalidomide in 40 patients who have mesothelioma, of whom 50% had received previous chemotherapy. Disease stabilization for longer than 6 months was reported in 27.5% of the patients (Baas et al., 2005). Pavlakis et al. (2003) evaluated thalidomide alone or in combination with gemcitabine/cisplatin in two parallel non-randomized phase II studies. Single agent thalidomide was administered to 22 patients who were not considered suitable for chemotherapy nor progressed during treatment with antineoplastic drugs, whereas gemcitabine plus cisplatin was given with thalidomide to 16 chemotherapy-naive patients. Disease stabilization for longer than 6 months was observed in 25% of the patients who received single agent thalidomide, while in the combination arm, a partial response rate of 14% was reported, and 32% of these patients achieved disease stabilization for longer than 6 months. Moreover, a non-significant trend suggested that higher baseline levels of VEGF correlated with a shorter survival in both arms. However, when administered as consolidation following first-line platinum-antifolate based chemotherapy, thalidomide did not improve outcome when compared to placebo (Baas et al., 2011).

Imatinib is a highly selective inhibitor of the bcr/abl mutated tyrosine kinase, as well as of both c-kit and PDGFRs. Several Phase II studies have been conducted with imatinib mesylate in MPM refractory to chemotherapy or chemonaive patients, but negative results were reported (Kumar-Singh et al., 1999; Millward et al., 2003; Villano et al., 2004; Mathy et al., 2005; Porta et al., 2007). *In vitro* and *in vivo* experiments demonstrated that STI-571 can cause MPM cell apoptosis and death through inhibition of the AKT/PI3K pathway and that it can also enhance MPM sensitivity to gemcitabine or pemetrexed (Bertino et al., 2007). Patients with MPM are currently being enrolled in a Phase I study of imatinib combined with cisplatin and pemetrexed (Anonymous, 2009h) and in a phase II study in association with gemcitabine to evaluate the efficacy of these compounds (Anonymous, 2009a).

Rapamycin, a natural macrolide approved as immunosuppressor, was found to exert anti-proliferative effects by inhibition of serine/threonine kinase, which in mammals is called mammalian target of rapamycin (m-TOR). Synthetic derivatives or “rapalogs” have been developed to improve the pharmacological properties of rapamycin: everolimus, temsirolimus, and deforolimus. Temsirolimus was evaluated in a phase I study of dose-escalation and no tumor response in patients with MPM was observed (Raymond et al., 2004).

Histone deacetylase (HDAC) inhibitors are novel anticancer agents that act by a variety of mechanisms. Histones are the core-proteins in the center of the DNA double helix. The histone proteins exist in either a non-acetylated transcriptional inactive configuration or an acetylated state that is open to gene transcription. The dynamic equilibrium between the acetylated and non-acetylated forms is mediated by histone acetyltransferase and HDAC (Marks et al., 2001). Agents that inhibit HDAC have recently demonstrated promising anticancer activity in early phase clinical trials. *Vorinostat* is a small molecule inhibitor of HDAC that is approved by the FDA for the treatment of advanced, relapsed, or refractory cutaneous T-cell lymphoma. In addition to its inhibitory effect on HDAC, vorinostat also acetylates several key cell signaling proteins that

play a role in regulating normal cell differentiation, apoptosis, and proliferation. Therefore, both histone and non-histone protein-mediated effects of HDAC inhibitors are thought to be responsible for their anticancer effects (Deroanne et al., 2002). Initial studies of vorinostat have demonstrated objective responses in patients with MPM. In the initial phase I studies with the oral formulation of vorinostat, 13 patients with advanced MPM were included (Krug et al., 2006). Twelve out of these patients had received prior systemic chemotherapy for MPM. Two objective partial responses were reported and the treatment regimen was tolerated well. These data form the basis for a large randomized clinical trial to compare vorinostat to placebo in pretreated patients. The primary end point is overall survival (Anonymous, 2009l). The mechanistic aspects of the efficacy noted with vorinostat in MPM are unclear. Because inhibitors of thymidylate synthase (TS) have demonstrated activity in MPM, it is conceivable that repression of TS and cytidine triphosphate synthetase by HDAC inhibitors could play a role. Another mechanism may be the induction of apoptosis, which has been demonstrated with preclinical studies of sodium butyrate, a HDAC inhibitor, in mesothelioma cell lines. HDAC inhibitors have also been shown to block angiogenic signaling by inhibiting VEGF-induced expression of VEGF receptors. Another HDAC inhibitor, *belinostat*, is being evaluated in a Phase II study as a second line therapy (Anonymous, 2009i).

The proteasome inhibitor bortezomib inhibits nuclear factor-kappa B and up-regulates pro-apoptotic BH3 proteins (Fennell et al., 2008). Proteasome inhibition induces apoptosis of mesothelioma cells *in vivo* and *in vitro* (Gordon et al., 2007; Sartore-Bianchi et al., 2007). On the basis of promising preclinical data, two phase II trials of *bortezomib* have been initiated in Europe. One trial is exploring single agent activity in the second line setting and in patients with a performance status of 2 in the first-line setting (Anonymous, 2009g). The second trial, conducted by the EORTC, has explored this agent in combination with cisplatin in the first-line setting (Anonymous, 2009f).

Other angiogenic growth factors expressed in this disease include transforming growth factor β , FGF1, FGF2, thrombospondin 1, methionine amino-peptidases, interleukin (IL)-6 and IL-8. High levels of VEGF and FGF2 or co-expression of TGF β , VEGF, FGF1, and FGF2 have been found to be associated with a poor outcome. MPM exhibits high levels of expression of the surrogate marker of hypoxia, hypoxia-inducible factor 1 α (Klabatsa et al., 2006).

Blockade of TGF- β is an new approach for mesothelioma. GC1008 is a human IgG4 kappa monoclonal antibody capable of neutralizing all mammalian isoforms of TGF- β (i.e., β 1, β 2, and β 3). GC1008 is a high-affinity antibody with dissociation constants (Kds) of 1.8, 2.8, and 1.4 nM for TGF1, 2, and 3, respectively. The anti-TGF Monoclonal Antibody GC1008 is currently investigated in relapsed MPM (Anonymous, 2010).

Dasatinib, a Src inhibitor, is currently evaluated in a phase II trial in pretreated patients and in another trial in patients with resectable mesothelioma (Anonymous, 2010; Anonymous n.d. a).

MESOTHELIN TARGETED IMMUNOTHERAPY

Mesothelin is a differentiation antigen whose expression in normal human tissues is limited to mesothelial cells lining the pleura, pericardium, and peritoneum. However, mesothelin is highly expressed

in several human cancers, including virtually all mesotheliomas and pancreatic adenocarcinomas, and approximately 70% of ovarian cancers and 50% of lung adenocarcinomas. Mesothelin gene expression in human cancers has been studied using serial analysis of gene expression (SAGE) tag analysis. High mRNA expression of mesothelin is found in mesothelioma, lung, ovarian, and pancreatic adenocarcinomas. In addition, immunohistochemistry has helped delineate the frequency and pattern of mesothelin protein expression in these tumors. These studies have been greatly facilitated by the commercial availability of a monoclonal antibody (mAb) 5B2 (Novocastra, Newcastle-on-Tyne, UK) that can detect mesothelin expression in paraffin embedded tissues. Mesothelin is highly expressed in epithelial malignant mesothelioma (**Figure 1**). In the original study by Chang et al. (1992), mesothelin expression was evaluated by mAb-K1 using frozen section tissues of patients with malignant mesothelioma. Out of the 23 pleural mesothelioma samples analyzed all 15 epithelial mesothelioma samples had mesothelin expression, while 4 sarcomatous mesotheliomas were negative. In the four samples with biphasic mesothelioma, only the epithelial component stained for mesothelin. Mesothelin expression in paraffin embedded mesothelioma tissue samples was studied by Ordonez (2003) using mAb 5B2. Out of the 55 mesothelioma specimens (44 epithelioid, three biphasic, and eight sarcomatoid) studied, mesothelin reactivity was noted in all epithelioid mesotheliomas and the epithelial component of biphasic mesotheliomas and none of the sarcomatous mesotheliomas expressed mesothelin. Although mesothelin is not a specific marker for mesothelioma a negative mesothelin immunostain strongly argues against the diagnosis of epithelioid mesothelioma (Ordanez, 2007). To determine whether a spontaneous humoral B-cell response to mesothelin is present in patients with mesothelin expressing cancers Ho et al. (2005) used a sensitive enzyme-linked immunosorbent assay (ELISA) to detect mesothelin-specific IgG antibodies in serum of patients with advanced mesothelioma and ovarian cancer. Elevated levels of mesothelin-specific antibodies were detected in the sera of 27 of 69 (39%) patients with mesothelioma and 10 of 24 (42%)

patients with epithelial ovarian cancer when compared with a normal control population. Mesothelin-specific antibodies were present at a higher frequency in patients whose tumors had strong mesothelin expression by immunohistochemistry. These results suggest that the immunogenicity of mesothelin is associated with its high expression on the tumor cells and serologic recognition of mesothelin is cancer related. The presence of a mesothelin-specific B-cell response in a significant proportion of patients with mesothelin expressing tumors supports on-going efforts to use mesothelin as a therapeutic cancer vaccine. Several agents with activity in preclinical models are being developed to target mesothelin: a recombinant immunotoxin (SS1P), a humanized monoclonal antibody (MORab-009) and an attenuated *Listeria* vector that encodes human mesothelin (CRS-207).

SS1P is a recombinant immunotoxin consisting of an anti-mesothelin Fv linked to a truncated *Pseudomonas* exotoxin that mediates cell killing (Chowdhury et al., 1998; Chowdhury and Pastan, 1999). After binding to mesothelin, the immunotoxin is internalized via clathrin coated pits, undergoes processing in the endocytic compartment and the immunotoxin fragment containing the ADP-ribosylation domain is transported to the endoplasmic reticulum and then translocated to the cytosol where it inhibits elongation factor-2 leading to inhibition of protein synthesis and ultimately cell death (Hassan et al., 2007). Recent studies have looked at the anti-tumor activity of SS1P in combination with radiation therapy or chemotherapy. Athymic nude mice bearing A431/K5 mesothelin expressing tumors were treated with radiation alone, SS1P alone or the two agents in combination (Chowdhury et al., 1998). The results of this study showed that mice treated with low-dose radiation and SS1P or high-dose radiation and SS1P had a statistically significant prolongation in time to tumor doubling or tripling compared with control, SS1P or radiation alone treated mice. Since radiation treatment increased the cell surface expression of mesothelin, it is possible that the increased anti-tumor activity of SS1P in combination with radiation is partly due to enhanced mesothelin expression, making the cells more sensitive to SS1P treatment. Given the non-overlapping toxicities and different modes of action of SS1P and chemotherapeutic agents, combining them could potentially result in increased anti-tumor activity in patients.

Two Phase I studies of SS1P have just been completed. These studies which were designed to test the safety, MTD, and pharmacokinetics of SS1P used two different strategies for SS1P administration. In one study SS1P was administered as an intravenous bolus infusion over 30 min (SS1P bolus infusion study) while as in the other study SS1P was given as a continuous i.v. infusion over 10 days (SS1P continuous infusion study). Most common toxicities were similar for both the bolus infusion and continuous infusion including hypoalbuminemia, weight gain, edema, and fatigue. Of the 33 evaluable patients treated, four had minor responses, 19 had stable disease (including two with resolution of ascites and died after 5 years after the therapy), while 10 had progressive disease (Hassan et al., 2007). Based on this study and in previously reported synergistic effects of SSP1 in combination with chemotherapy (Zhang et al., 2006), a phase II study is planned.

MORab-009 is a high-affinity chimeric (mouse/human) monoclonal IgG1/ κ with high-affinity and specificity for mesothelin. The heavy and light chain variable regions of mouse anti-mesothelin

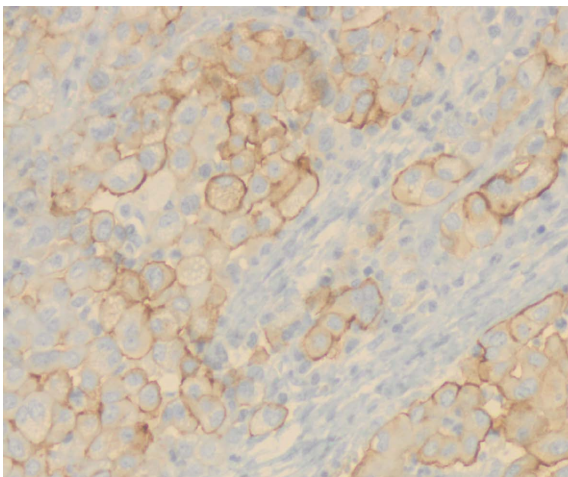


FIGURE 1 | Mesothelin expression detected by IHC in tissue specimens of patients with MPM (x250).

scFv (obtained by panning on mesothelin-positive cells a phage display library made from splenic mRNA of a mouse immunized with mesothelin cDNA) were grafted in frame with human IgG1 and κ constant regions. Since MORAb-009 is a chimeric antibody containing only the mouse sequences that recognize human mesothelin, it should be less immunogenic and allow repeated administration to patients. Laboratory studies show that MORAb-009 kills mesothelin expressing cell lines via antibody dependent cellular cytotoxicity (ADCC) and in addition it inhibits the binding of mesothelin to CA-125. Based on these preclinical studies a Phase I clinical trial of MORAb-009 has been completed (Anonymous, 2009d).

The rationale for mesothelin as a tumor vaccine is based on studies showing that mesothelin can elicit a strong CD8+ T-cell response in patients (Thomas et al., 2004). One of the mesothelin cancer vaccines in advanced stages of clinical development is CRS-207 (*Lm* Δ actA/ Δ inlB/*hMeso*). This vaccine utilizes a live-attenuated strain of the bacterium *Listeria monocytogenes* (*Lm*), a facultative intracellular bacterium, as the vector 40 (Brockstedt et al., 2004). The engineered vector CRS-100, has deletions of the two genes that encode the virulence determinants actA and internalin B (inlB), which results in a greater than 1000-fold decrease in virulence compared to the wild type *Lm*. CRS-207 is a live-attenuated *Lm* vaccine strain based on CRS-100 that encodes human mesothelin. Preclinical studies show that CRS-207 elicits human mesothelin-specific CD4+/CD8+ immunity in mice and in cynomolgus monkeys and exhibits therapeutic efficacy in tumor bearing mice (Giedlin et al., 2007). A Phase I clinical trial of CRS-207 for the treatment of patients with mesothelin expressing cancers is on-going (Anonymous, n.d. j). The utility of mesothelin as a tumor vaccine came from a clinical trial conducted by Jaffe and colleagues that involved vaccination of pancreatic cancer patients with GM-CSF transduced pancreatic cancer cell lines (Jaffee et al., 2001). Out of the 14 patients treated on this study three developed a post-vaccination delayed-type hypersensitivity (DTH) response to the autologous tumor, that was associated with prolonged survival (Yokokawa et al., 2005). In another vaccine study, T-cell lines derived from the native or the agonist mesothelin epitope were shown to lyse mesothelin expressing and HLA-2 positive pancreatic cancer, ovarian cancer, and mesothelioma cell lines (Yokokawa et al., 2005). All these studies support the potential utility of mesothelin in peptide and/or vector-mediated immunotherapy protocols for the treatment of cancers that highly express mesothelin.

VACCINE APPROACHES

Vaccine approaches are also under investigation for the treatment of MPM. Wilms tumor associated gene (WT)-1 is a transcription factor expressed in tissues of mesodermal origin during embryogenesis. Up-regulation of WT-1 has been linked with tumorigenesis of various malignancies including mesothelioma and is an attractive target for immunotherapy (May et al., 2007). Therefore, WT-1 peptide epitopes that stimulate T-cell immunity are currently under evaluation for the treatment of mesothelioma. Preliminary results from on-going studies have documented the safety of this vaccine. Interesting preliminary results were observed after administration of *Mycobacterium vaccae* in a limited number of patients. This needs to be confirmed before further exploring this treatment. A randomized study of adjuvant WT-1 analog peptide vaccine in

patients with MPM after completion of combined modality therapy is on-going (Anonymous, n.d. h). Mesothelin as tumor vaccine has been described in the previous section.

DENDRITIC CELL BASED IMMUNOTHERAPY

Immunotherapy is a promising approach in the treatment of cancer. It tries to harness the potency and specificity of the immune system to attack cancer cells. The aim is a non-toxic treatment with minor side-effects and a long-lasting immunological memory. One approach of immunotherapy uses dendritic cells (DC) to present tumor-associated antigens (TAA) and thereby generate tumor-specific immunity (Steinman and Dhodapkar, 2001; Banchereau and Palucka, 2005). DC are extremely potent antigen-presenting cells specialized for inducing activation and proliferation of CD8+ cytotoxic T lymphocytes (CTL) and helper CD4+ lymphocytes. Hegmans et al. (2005) demonstrated in a murine model that immunotherapy, using pulsed DC, may emerge as a powerful tool to control mesothelioma outgrowth. They showed that mesothelioma is infiltrated by immune effector cells but also contains cytokines and regulatory T-cells that suppress an efficient immune response. Immunotherapy of mesothelioma might be more effective when combined with drugs that eliminate or control regulatory T-cells (Hegmans et al., 2006). They have also demonstrated that the efficacy of immunotherapy was dependent on the tumor load. The most beneficial effects were established at early stages of tumor development. This is in agreement with the current knowledge of the effect of immunotherapy in other tumor types (Cranmer et al., 2004). On the basis of these preclinical animal studies, a clinical trial in which autologous tumor lysate-pulsed DC were administered intra-dermally and intravenously in mesothelioma patients after cyto-reductive therapy with chemotherapy is now completed. Patients received 50×10^6 mature DC pulsed with tumor lysate and keyhole limpet hemocyanin (KLH) every 2 weeks for a total of three injections. The administration of DCs loaded with autologous tumor cell lysate to patients was safe. Local skin reactions were seen at the site of the intradermal injection suggesting that some form of immunity was induced. There was no clinical or radiological evidence of any autoimmunity. Distinct immunological responses to the surrogate marker KLH were induced by the vaccinations, both *in vitro* as *in vivo*. Importantly, anti-tumor cytotoxicity activity against autologous tumor cells was measured in the blood of patients. An increase in systemic CTL activity was seen in a subset of treated patients (4 out of 6). Multiple vaccinations were necessary as the increase in CTL activity was seen only after 3 vaccinations for most of the patients in this assay. DC loaded with autologous tumor cell lysate administered to patients was considered safe and feasible and no adverse effects were observed. Anti-tumor immune responses were detected in a few patients with mesothelioma after DC-immunotherapy. Whether this has a beneficial effect in improving survival will be the subject in successive studies. Influencing the immunosuppressive cells (Tregs, M2 macrophages, and MDSC), cells abundantly present in the tumor environment, and their subsequent effect on DC-mediated anti-tumor responses, seems of critical importance for future clinical trials. Also other sources of antigens to pulse DC must be investigated to make DC-immunotherapy more accessible for larger numbers of patients to perform comparative studies (Figure 2).

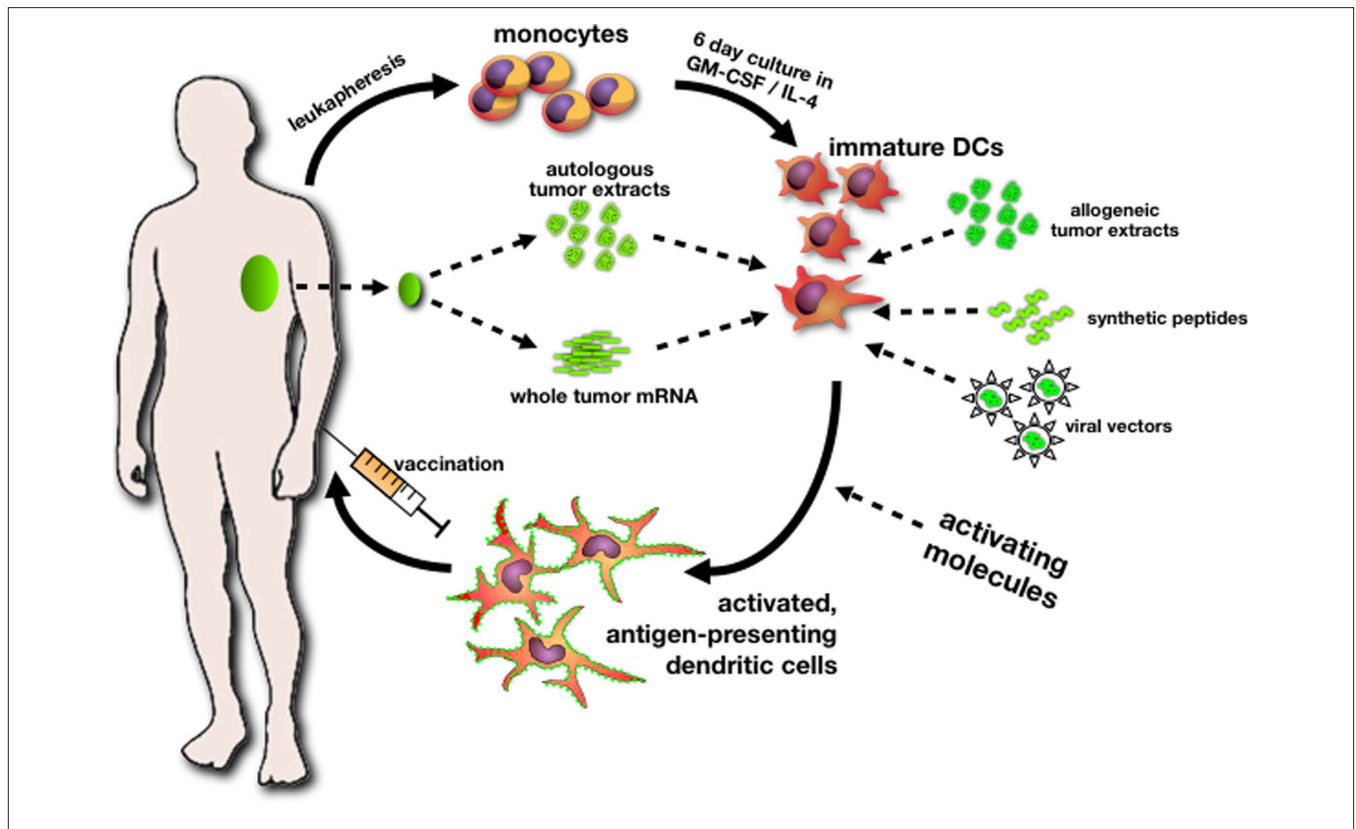


FIGURE 2 | A general workflow for the production of autologous dendritic cell vaccines for cancer immunotherapy. Monocytes, harvested from a leukapheresis, are differentiated *in vitro* under GMP-conditions into immature dendritic cells. The prototypical cytokines used for the generation of monocyte-derived DCs are GM-CSF and IL-4. Immature DCs can subsequently be loaded with tumor-derived antigens using different approaches: DCs can phagocytose proteins from autologous tumor lysate or be electroporated with tumor-derived

mRNA. When access to autologous tumor is too limiting, DCs can be loaded with allogeneic tumor proteins, peptides derived from putative tumor-associated antigens (TAAs), or transduced with viral vectors encoding TAAs. A crucial final step in the whole process is the activation/maturation of DCs, typically using Toll-like receptor ligands and/or a cocktail of activating cytokines. The resulting activated, tumor antigen-presenting DCs constitute the vaccine. After injection, DCs migrate to draining lymph nodes and activate tumor-specific cytotoxic T-cells.

GENE THERAPY

Malignant pleural mesothelioma represents a good potential target disease for gene therapy. The disease is localized until late, is easily accessible, current therapies are inadequate and there is some evidence of immune responsiveness. Clinical trials of patients with MPM have established the safety of the intra-pleural delivery of replication-deficient adenoviral vectors expressing the suicide gene, herpes simplex thymidine kinase, followed by the administration of ganciclovir, an antiviral drug. Some evidence indicates that this approach induces an effective anti-tumor immune response (Serman et al., 1998, 2005). Moreover, intra-pleural interferon- β gene transfer with a replication-defective adenoviral vector may potentially be a useful approach for the generation of anti-tumor immune responses in MPM patients (Serman et al., 2007). A significant obstacle to these approaches is the limited distribution of the non-replicative vectors within the tumor mass, even after direct intra-tumoral administration. Therefore, more efficient strategies for the virus to spread within tumors may be required to increase the clinical benefit. In a recent study, it was shown that intrathoracic administration of telomerase-specific oncolytic viruses induced significant anti-tumor effects against both pre-established and established pleural dissemination of human MPM (Watanabe

et al., 2010). A phase I, dose-escalation study of telomerase-specific oncolytic adenovirus, OBP-301, is currently underway in the United States to assess the treatment feasibility and to characterize its pharmacokinetics in patients with advanced solid tumors. Phase II studies of telomerase-specific virotherapy in MPM patients are warranted. An phase I intra-pleural gene transfer study for pleural mesothelioma (IFN- α , SCH 721015, Ad.hIFN- α 2b) is on-going (Anonymous, n.d. c). The effect of Ad. IFN is enhanced by combining with chemotherapy and phase I trials with this combination are in development.

INVESTIGATIONAL SURGICAL APPROACHES

In MPM, the role of surgery remains controversial and should be further explored. Although the multimodality treatment procedure seems feasible, overall treatment time is long and psychological distress is considerable. Subgroup analysis of a large Scandinavian phase II combination chemotherapy trial shows a median overall survival of 22 months in patients with good performance status, epithelioid subtype, stage I–II and aged 70 years or less, equivalent to survival in patients subjected to multimodality treatment (Hillerdal et al., 2008). These findings stress the importance of a large prospective multicentre, in which operable patients with early

stage resectable MPM are randomly assigned to a surgical and a non-surgical management (Treasure et al., 2004). The feasibility of this approach has been explored in the UK MARS 1 trial, in which the randomization is between EPP followed by PORT and any palliative treatment, including pleurodesis, following an induction treatment with chemotherapy (Treasure et al., 2009). The results of the feasibility part of this trial have recently been released and show no difference in survival between both treatment arms (Treasure et al., 2010). A large retrospective uncontrolled series reports that P/D might prolong survival as compared to EPP and that a less invasive procedure might hence be preferable in selected patients, provided it is standardized (Flores et al., 2008). In a systematic review of 1270 patients who had undergone lung-sparing surgery for mesothelioma (Teh et al., 2010), overall survival was comparable with the outcome reported in historical series including EPP. It is expected that a large European multicentre randomized trial will be conducted in the coming years, addressing the role of any tumor resection in MPM. Whether the latter will include EPP remains to be determined (Rusch, 2009).

INVESTIGATIONAL RADIOTHERAPY APPROACHES

As in NSCLC, the role of PORT in MPM is controversial and based on a single uncontrolled retrospective series. This additional value of PORT is being addressed in an on-going Swiss study, in which eligible patients are randomized after EPP between observation and hemi-thoracic PORT (Swiss Group for Clinical Cancer Research, 2009). Pleural IMRT allows administering a radical dose of radiotherapy to a MPM with intact lung (Rosenzweig et al., 2009). The role of IMRT with chemotherapy is presently being investigated in patients with irresectable disease (Anonymous, 2009k). Currently a study that looks at whether giving a short intense course of chest radiation just prior to surgery will sterilize these tumor cells and thus, avoid or reduce contamination of the areas outside the chest cavity is on-going. The investigators hypothesize that short neoadjuvant (pre-operative) hemi-thoracic IMRT, followed by immediate planned EPP (\pm adjuvant chemotherapy) will reduce the risk of intra-operative seeding and reduce the incidence of distant metastatic disease (Anonymous, n.d. i).

Another trial explores the use of new radiation technology, tomotherapy, to treat mesothelioma more aggressively than has been possible before. Tomotherapy's ability to treat unusual shaped tumors, particularly when they are wrapped around sensitive normal tissues (the lung), enable higher doses of radiation to be used and this may improve its effectiveness (Anonymous, n.d. k).

An improved response has been seen in several studies where hyperthermia was added to radiotherapy. However, further investigation of this technique, which is not widely available, is required.

ARRAY TECHNOLOGY IN MESOTHELIOMA

With the advent of gene expression profiling frequent use of arrays has been carried out on MPM patient material, in attempts to identify profiles which may be predictive, prognostic or give information on treatment response (predictive of personalized therapy). Other groups have attempted to use gene expression microarrays to identify potential MPM biomarkers or important pathways which may be important for MPM pathogenesis. One of the problems identified with the use of array technology in MPM, has been the

lack of concordance between the various predictive or prognostic studies (Gordon et al., 2003, 2005a; Pass et al., 2004; Glinsky et al., 2005; Lopez-Rios et al., 2006) Nevertheless, several of the genes identified in these predictive array studies have also shown up in other MPM array studies. Meta-analysis of the different mesothelioma studies may provide more robust prognostic genes which could be subsequently validated.

One emerging subset of genes which has been shown to be altered in mesothelioma concerns the insulin-like growth factor axis (Lee et al., 1993). With microarray analysis, several members of this axis have also been shown to be altered confirming the importance of this pathway in mesothelioma. Two commonly down-regulated genes from the IGF-axis in mesothelioma are *IGFB-4* and *IGFBP-5* (Kettunen et al., 2004), mainly over-expressed genes include *IGFBP-2*, *IGFBP-3*, *IGFBP-7/MAC25*, and an exon specific isoform of IGF-I (IGF-I, exon 1A; Hoang et al., 2004; Mohr et al., 2004; Gordon et al., 2005b; Anonymous, n.d. g) be noted that *IGFBP-3* is another gene whose overexpression has also been linked to poor outcome tumors (Gordon et al., 2005b) indicating that a comprehensive analysis of the IGFBP family may have clinical value in MPM. A Phase II Study of IMC-A12, an antibody that is designed to block the effects of a protein called Type I Insulin-Like Growth Factor (IGF-1R), in patients with mesothelioma who have been previously treated with chemotherapy is on-going (Anonymous, n.d. g).

CONCLUSION

The last decade has seen some important changes in the management of mesothelioma. We now have active first-line chemotherapy available, which will not only moderately increase survival but will also help in relieving symptoms. But most of patients will have relapse after first-line chemotherapy and their survival is poor. The molecular biologic research should focus on mesothelioma-specific pathways and biomarkers; this is the only way to move forward and to explore novel, more active therapeutic options and better treatments for this disease. A small proportion of patients might benefit from more aggressive (surgical) interventions with radical or even curative intent. It is our duty as physicians to inform our patients about all treatment options available but also to protect them from potential harmful or useless therapies. As with any rare disease, referral of the patients with MPM to a center with extensive experience and expertise with this disease is recommended to enhance the probability of accruing these patients into clinical trials.

Recent progress has reshaped the clinical landscape in the treatment of MPM. We have now more effective chemotherapy and from current evidence, it is clear that histone deacetylase inhibitors represent a potentially new treatment modality in MPM. Among current investigational drugs, mesothelin targeted therapies, dendritic cell based immunotherapy, and gene therapy hold promise and should be further explored. Despite these, actual treatment is still amenable to improvement. Several factors have hampered the development of more effective regimens for mesothelioma. MPM is uncommon, is heterogeneous, staging is unreliable, response assessment is difficult and most drugs do not work. For the staging, the International Mesothelioma Interest Group are actually collaborating with the IASLC to include MPM in its proposals for the eighth edition of

TNM classification. The ability to measure reproducibly tumor response to treatment is vital in the development of new drugs and therapeutic combinations, particularly for the conducting of phase II studies. Conventional response criteria have always been difficult to apply to malignant mesothelioma due to its unique pattern of growth. Because the selection of measurement sites in mesothelioma is difficult, RECIST criteria could be applied differently by different investigators and that's why the Modified RECIST criteria have been developed. Based on the complex growth pattern of MPM, response evaluation in this cancer entity is still challenging. Results on value of fluoro-2-deoxy-D-glucose and positron emission tomography imaging [SUV mean, tumor lesion glycolysis (TLG), and tumor volume (PETvol)] in response assessment in MPM are promising.

Where do we go from here with the systemic therapy for MPM? We need better drugs, probably by more accurate preclinical investigation and we have to use better the drugs we have: in maintenance therapy, in special populations, in multimodality setting. More selectivity regarding the "promising" drug we choose to move from the bench to the clinic and fewer "me too" trials are warranted. Better designed trials that are adequately powered, multicentre, preferable with randomized phase II design to balance for heterogeneity, with appropriate endpoints (PFS, OS, QoL) and with correlative studies built in, are mandatory. Methods to assay individual tumor characteristics are warranted in order to avoid toxicity in patients who may not respond to treatment and losing precious time in a disease associated with a short survival. Drug resistance profiles have been reported to various malignant diseases including NSCLC, SCLC, breast, ovarian, colon, esophageal, and carcinoid tumors. Recently the feasibility of performing off-site *in vitro* drug resistance assays on resected mesothelioma specimens is reported.

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