# Alternative Options in the Management of Malignant Pleural Mesothelioma

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#### Abstract

Malignant pleural mesothelioma is a solid, locally aggressive tumor that has been linked to asbestos exposure. Without treatment MPM is associated with a poor median survival, ranging from 4 to 12 months. Extrapleural pneumonectomy offers better local control compared to pleurectomy/decortication. Chemotherapy combined with IL-2 and radiation provides some palliation. However, unsatisfactory results of these approaches have led clinicians to pursue novel therapeutic options. Local photodynamic therapy (PDT) has been studied with pleurectomy or extrapleural pneumonectomy. Intrapleural IFN-I radiosensitization and targeted immunotherapies may downstage tumors preoperatively. Gene therapies can sensitize tumor cells to antiviral drugs and may be used as a neoadjuvant therapy or to destroy residual tumor after resection. Inhibition of angiogenic growth factors or their receptors can slow tumor growth. Intracavitary hyperthermic chemotherapy, photodynamic therapy, vaccination, immunotherapy, and gene therapy are relatively new options with potential to be integrated into multimodality approach.

## INTRODUCTION

Malignant pleural mesothelioma (MPM) is an aggressive disease of the pleura. This rare tumor predominantly affects men over 50 years of age (male to female ratio 3:1) and is associated with a long latency period between asbestos exposure and tumor manifestation. MPM is associated with a poor median survival, ranging from 4 to 12 months; however, a multimodality approach can improve the survival [,].

The clinical presentation of MPM is highly variable making it difficult to diagnose and intervene promptly. The time between presentation and diagnosis is typically 2 to 5 months and delay reduces median survival. MPM is unilateral in 95% of cases, occurring more often on the right (60% of cases) [2]. Early symptoms include dyspnea, chest pain, fever, and pleural effusion. Advanced stages are characterized by weight loss, ascites, and/or chest wall deformities. Prognosis is multifactorial and depends on age, performance status, hematologic parameters, and tumor histology [6, 7]. Clinical classification and mode of treatment are both independent predictors of outcome for patients with MPM [3]. There is still no universally standard approach for its management [4], and failure of conventional therapies has led the clinicians to attempt multimodality approach with inclusion of novel options.

Lately, a multimodality approach including extrapleural pneumonectomy (EPP) or pleurectomy followed by adjuvant chemoradiation improves survival and quality of life [2, 4, 5]. A 45% 5-year survival rate has been reported for a subgroup of patients with early-stage disease, the absences of mediastinal lymph node involvement, and epithelial histology who undergo EPP followed by adjuvant chemoradiation [5]. Recurrence of the tumor is mostly local and isolated distant recurrences are less common [6]. Efforts to decrease the risk of local recurrence after EPP and pneumonectomy/decortication (P/D) have included intrapleural and intravenous chemotherapy, brachytherapy, and external beam radiation therapy.

The lowest rate of local recurrence after EPP reported is 13%, with a 4% local-only recurrence rate, as published by Rusch et al. who used adjuvant 54 Gy hemithorax radiation  $[_7]$ . Baldini et al. reported a 50% local recurrence rate, with a 13% local-only recurrence rate, after trimodality therapy  $[_4]$ . Currently no randomized trials evaluating the various surgical or adjuvant therapeutic approaches have been performed  $[_6]$ . Specific therapeutic options, including intrapleural chemotherapy, photodynamic therapy, gene therapy, immunotherapy, vaccination and tyrosine kinase inhibitors have demonstrated some encouraging results, but have yet to be evaluated fully in clinical trials  $[_8]$ , however,

these novel approach have a potential to be included in a multimodality approach.

# PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) is a novel complementary therapy for MPM using the light sensitive compound photofrin (meta-tetrahydroxyphenylchlorin; mTHPC) to destroy malignant cells. Normal cells are able to excrete the photofrin prior to activation; however, malignant cells lack this ability and are therefore selectively targeted. Clinical use of PDT requires the use of a photosensitizing agent, usually injected 48 hours prior to surgery, and a wavelength of light specific to the absorption characteristics of the sensitizer. After exposure to appropriate light, photofrin is activated, forming free radicals that destroy the cells in which it is contained. This process requires high oxygen concentration at the site and the tumor response correlates strongly with the drug-light interval. Oxygen consumption by photochemical reaction during PDT can cause rapid local oxygen depletion, which could be self-limiting in efficacy of this therapy.

PDT has limited penetration making it an ideal treatment for tissue surfaces and body cavities after surgical debulking [<sub>9</sub>]. Combining PDT with EPP in 18 pigs with MPM showed selective destruction of mesothelioma xenografts without damage to intrathoracic organs [<sub>10</sub>]. Takita et al. reported a median survival of 21 months for Butchart stage I and II tumors in a phase II trial consisting of either P/D or EPP followed by PDT administered to the pleural space [<sub>11</sub>]. However, at the National Cancer Institute (NCI), Pass et al. found no survival advantage (median survival 14 months) or change in the time interval until tumor recurrence in a phase III trial (n=48) [<sub>12</sub>].

A combination of pleuropneumonectomy and mTHPC PDT resulted in local control of disease in 50% of the cases, with a median survival of 10 months [ $_{13}$ ]. In a phase I clinical trial (n=26) combining Foscan (temoporforin)-mediated PDT after surgical debulking by EPP (n=7) or P/D (n=19), toxicities included burns and skin photosensitivity. There were two PDT-related deaths. The authors advocated combining Foscan-mediated PDT with surgery [ $_{14}$ ].

# **IMMUNOTHERAPY**

Various immunomodulators, including interferons (IFN-?, IFN-?) and interleukins (IL-1, IL-2) have been investigated in patients with MPM [15]. IL-2 and IFN-? have been shown to stimulate the inflammatory response and have

a direct cytotoxic effect on mesothelioma cells in vitro. These agents facilitate cellular differentiation and activate T lymphocytes and natural killer cells in vivo [16, 17]. Boutin et al. administered 40 million units of recombinant IFN-? into the pleural space in patients with Butchart's stage I and II MPM. There were 8 complete responders as documented by surgical biopsy and 9 additional patients had at least a 50% reduction in tumor mass. Overall response rate was 20% [18]. A phase II trial reported a response rate of 14% after intrapleural injection of activated macrophages and IFN-?, which was far below expectations. The median survival of patients including those who also received chemotherapy was 29.2 months [19]. Palliative effects of intrapleural instillation of IL-2 following needle thoracentesis of pleural effusion were experienced by 90% of patients (28/31) with MPM [20]. In a phase II clinical trial (n=28), using IL-2 for maintenance therapy, the median survival was 13 months and the median time to progression of disease was 7 months [21]. Maintenance therapy with IL-2 after completion of chemotherapy could potentially delay tumor recurrence.

## VACCINATION

Although MPM is not classically an immunogenic cancer, there is abundant evidence supporting immune recognition. Malignant mesothelioma patients and asbestos-exposed individuals without malignant mesothelioma have impaired immune systems. Western blot analysis of immunoglobulin G (IgG) antibodies are reactive with a variety of autoantigens in many patients with MPM [22]. Immunotherapy and vaccination is therefore a potential therapeutic option.

Delayed tumor growth after debulking surgery followed by vaccination with B7-1 and granulocyte-macrophage colony stimulating factor (GM-CSF) has been reported [ $_{23}$ ]. Autologous MPM tumor cell lysate produced from resected tumor, given subcutaneously with recombinant GM-CSF has shown some anti-tumor effects. In particular, Powell et al. reported an anti-MPM response in 33% of patients (7/21) after vaccination therapy. Although the authors did not find any CT evidence of complete or partial response in their series, 7 patients had stable disease for the duration of the trial [ $_{24}$ ]. Risks include inducing major histocompatibility complex (MHC) and cytotoxic T lymphocyte responses.

Vaccination seems to be a promising contributor to the multimodality approach to MPM, but further investigation into optimal vaccination conditions is needed  $[_{25}]$ .

When tumor specific antigens are identified, recombinant

technology offers additional ways of selectively targeting a tumor. Mesothelin is a cell surface antigen expressed on most mesotheliomas. Potent bacterial toxins have been used to create recombinant immunotoxins, chimeric proteins in which the variable (Fv) portion of a tumor-specific monoclonal antibody is genetically fused to a bacterial toxin. SS1(dsFv)-PE38 immunotoxin (SS1P, anti-mesothelin dsFv-PE38) is produced by mutagenesis of anti-mesothelin Fv sequences fused with a truncated 31 kDa portion of Pseudomonas exotoxin A. It has been safe and effective in preclinical studies [26].

SS1P targets the mesothelin antigen expressed on mesothelioma, ovarian cancer, and pancreatic cancer. In cell culture, SS1P has potent cytotoxic activity against mesothelin-positive cells [27]. However in vivo results have been more limited. This low activity is believed to be due to the low entry of the immunotoxin into solid tumors. The combination of Taxol and SS1P has a very potent and synergistic antitumor activity in mice, but it was not evident on the same tumor cells growing in tissue culture. Therefore the synergy must involve an indirect effect on the tumor cells in vivo [28].

Hassan et al. evaluated SS1P in a phase I study of 9 mesothelin positive cancer patients in 2002. All patients except one developed antibody to SS1P after one course. Minor responses including regression of malignant ascites were also observed. Toxicities included a decline in serum albumin with weight gain and edema occurred in two patients. Asymptomatic pleural effusion occurred in two patients. Other adverse effects included fever and chills, myalgia, fatigue, nausea, transient shortness of breath, and lymphopenia. No cardiac function changes were noted  $[_{29}]$ . In 2007 Hassan et al. reported that SS1P is well tolerated with pleuritis as the major dose limiting toxicity (DLT) in a series of 34 patients with mesothelin-positive tumors, 59% of whom had mesothelioma (mesothelioma (n=20), ovarian cancer (n = 12), and pancreatic cancer (n = 2)). The maximum tolerated dose (MTD) was 18 mcg/kg/dose. DLTs at this concentration included grade 3 urticaria (n=1) and grade 3 vascular leak syndrome (n=2). Grade 3 pleuritis occurred in 1 of 9 patients at 45 mcg/kg and in both patients treated with 60 mcg/kg. Of the 33 patients evaluated, 19 had stable disease including 2 with resolved ascites, 4 had minor responses, and 10 had progressive disease [30].

# **GENE THERAPY**

Gene therapy is a novel and upcoming approach in the

treatment of mesothelioma. Promising viral vectors in this regard are replication-competent adenoviruses such as mutants of the herpes simplex virus type I (HSV-I) [<sub>31, 32</sub>]. Oncolytic HSVs used for gene therapy are genetically engineered replication-competent viruses that selectively target tumor cells while sparing normal host tissue. The goal is to infect mesothelioma cells with the virus to sensitize them to antiviral drugs, such as ganciclovir (GCV).

All three oncolytic strains of HSV (G207, NV1020, and NV1066) have been shown to be highly effective against MPM cell lines resistant to chemotherapy and radiation. Prolonged survival of patients with advanced disease has been reported with NV1066 [<sub>33</sub>]. In contrary to its wild type form, NV1066 lacks the gene ?(1)34.5 which encodes for ICP23.5. ICP23.5 plays a crucial role in cell replication and induces production of growth factors as well as a DNA damage-inducible antitumor protein (GADD34). Cisplatin selectively enhances the cytotoxicity of NV1066 by up regulating GADD34 expression which results in increased viral replication and host cell death [<sub>33</sub>].

The herpes simplex thymidine kinase (HS-tk) gene has been used to introduce a toxic or suicidal gene into mesothelioma cells [ $_{34}$ ]. Injection of adenoviral vectors carrying the HS-tk gene (AdHS-tk) into the pleural space can target the tumor cells. In a recent study (n=21) with intrapleural injection of a non-replicative AdHS-tk in combination with systemic GCV demonstrated some efficacy [ $_{35}$ ].

Using the adeno-associated virus rAAV-2, nearly complete eradication of transduced and GCV-treated mesothelioma cell lines was achieved. rAAV-2-based gene therapy may offer a new approach for locoregional treatment of mesothelioma [<sub>36</sub>]. However, more experimental and clinical data are needed before this approach can be considered for widespread use in the therapy of MPM.

Induction of apoptosis in tumor cells is another treatment strategy. The bcl-2 family genes are major determinants of antiapoptotic activity of cells. Bcl-2 and Bcl-xL are over expressed in mesothelioma cells and play a role in chemoresistance. Down regulation of either Bcl-xL alone or Bcl-xL and Bcl-2 simultaneously with antisense oligonucleotides 4259 or 4625, respectively, lowers the apoptosis threshold in mesothelioma cells [37] and sensitizes them to the cytostatic effects of cisplatin and gemcitabine [37,38:39].

Falleni et al. reported recently that apoptotic effects in MPM

are linked more significantly to increased levels of Survivin than to variations in bcl-2 family expression. Progressive accumulation of survivin in malignant cells supports a role in pathogenesis of MPM. Survivin overexpression may also contribute to chemoresistance.. Antisurvivin oligonucleotides induce apoptosis in the survivin-positive mesothelioma cells offering another gene based approach [ $_{40}$ ].

# ANGIOGENESIS AND TARGETED THERAPY

When a tumor begins to outgrow its blood supply, resultant hypoperfusion of the tumor causes hypoxia, which stimulates production of hypoxia inducible transcription factor (HIF1). This in turn stimulates expression of growth factors including vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF). Both are autocrine growth factors which are overexpressed in MPM. Epidermal growth factor (EGF) and its receptor provide another pathway which plays a major role in angiogenesis. Mutation and/or overexpression of growth factors and TK receptors shift the balance from normal vasculogenesis to tumor angiogenesis, a universal process for all tumors, including MPM [41,42,43,44,45,46,47,48].

VEGF exerts its effect through TK receptors, mainly VEGFR-1 and VEGFR-2. Angiogenesis is stimulated by the induction of endothelial cell proliferation and migration to tumor tissue resulting in formation of new blood vessels [49]. VEGF is an independent prognostic factor in MPM and an elevated level within mesothelial cells is suggestive of poor outcome [50].

Blocking these signaling pathways could limit tumor growth. Cytotoxic recombinant drugs which selectively target these cytokines are potential agents for this propose [48, 51]. PDGF TK inhibition blocks growth factors and slows cellular proliferation [52]. Antibodies to VEGF and VEGF-C and their receptors VEGFR-2 and VEGFR-3, respectively, can be synergistic in inhibiting mesothelioma cell growth [43]. Recent clinical treatments suggest that most inhibitors of VEGF and/or EGFR receptors exert their therapeutic effect through targeting and inhibiting multiple pathways [53].

Current tyrosine kinase inhibitors (TKIs) with antitumor activity include imatinib mesylate (Gleevec), gefitinib (Iressa), erlotinib (Tarceva), lapatinib, canertinib, semaxinib, vatalanib, sorafenib, sunitinib (Sutent), and leflunomide [54].. These are currently being investigated in phase II and III clinical trials [65, 66]. Sunitinib (SU11248) is an orally bioavailable inhibitor that affects multiple TK receptors involved in tumor proliferation and angiogenesis, including VEGFR-1, 2, and 3, PDGFR-? and ?, KIT, RET receptors, and TJ receptors [55]. Sunitinib has demonstrated good results with gastrointestinal stromal tumors (GIST) [56], acute myeloid leukemia (AML) [57], and renal cell carcinoma (RCC)  $[_{58}]$ . It has been shown to inhibit the VEGF-dependent mitogenic response of endothelial cells [59], prevent angiogenesis [59, 60], and reduce the risk of metastatic spread of lung cancer in an animal model  $[_{60}]$ . Combined blockade of VEGF and TK receptors seems to be more effective in preventing tumor progression than either alone [61, 62]. The most commonly reported adverse effects are mild and include fatigue, gastrointestinal changes (diarrhea, nausea, vomiting, stomatitis, and dyspepsia), anorexia, and hypertension. Hematologic complications include neutropenia, thrombocytopenia, anemia, and leukopenia [54, 55, 63, 64]. Hand-foot syndrome and skin discoloration are also seen [58].

Gefitinib decreases VEGF expression both by decreasing Sp1 binding to the proximal core VEGF promoter, downregulating HIF-1alpha expression, and inhibiting EGFR [<sub>67</sub>]. Gefitinib and erlotinib decrease c-fos mRNA levels in cell lines (A431, CAL27, and HN11) [<sub>68</sub>]. In a Cancer and Leukemia Group B phase II trail (n=43), gefitinib was administered to patients with untreated malignant mesothelioma (500 mg p.o, daily for 21 days). One patient (2%) had a complete response, 1 (2%) had a partial response, 21 (49%) had stable disease lasting two to eight cycles, 15 (35%) had progressive disease, and 5 (12%) had early deaths. One-year survival was 32%. EGFR expression score by immunohistochemistry done in 28 patients showed that although 97% had EGFR overexpression, gefitinib was not very effective in malignant mesothelioma [<sub>69</sub>].

Bevacizumab (Avastin), a recombinant humanized monoclonal antibody directed against VEGF, has shown some promising results [70]. Kindler et al. compared the efficacy of gemcitabine/cisplatin plus bevacizumab with gemcitabine/cisplatin plus placebo in patients with malignant mesothelioma in a multicenter, double-blind, placebo-controlled randomized phase II trial. Of 102 patients enrolled, 97 were evaluated (47 with bevacizumab and 48 with placebo). Patient characteristics were similar in both groups. The study showed that combination gemcitabine/cisplatin plus bevacizumab was well tolerated by patients. Major toxicities included neutropenia, anemia, thrombocytopenia, epistaxis, proteinuria, hypertension, and

#### thrombosis [43].

However it was reported at the 2007 ASCO meeting that the results of the same trial show nor significant survival benefit nor improved response for adding bevacizumab to a gemcitabine/cisplatin regimen. Instead high VEGF level was associated with poorer prognosis. This conclusion was supported by additional findings presented in the same meeting. For example, Karrison et al. reported in a phase II trial (n=108) that high plasma VEGF level is associated with worse survival [71].

Imatinib is an inhibitor of the protein TK Bcr-Abl and PDGFR-? and ?. It can be administered orally and has a bioavailability of 98% [ $_{72}$ ]. In a recent study, monotherapy with imatinib (starting dose of 400 mg per day taken orally, up to a maximal dose of 800 mg) did not significantly improve the survival (mean survival 398 days) in a series of 25 patients with MPM [ $_{73}$ ]. Secondary mutations in the TK domain of the KIT receptor may contribute to imatinib resistance [ $_{74}$ ]. The authors suggested a combination with gemcitabine and cisplatin which should be investigated in clinical trials [ $_{73}$ ].

## INTRAOPERATIVE HYPERTHERMIC CHEMOTHERAPY

Another novel approach in the treatment of MPM is the use of intraoperative intracavitary hyperthermic chemotherapy (heated chemotherapy). The cytotoxic activity of hyperthermia has been reported by Stehlin who pioneered the use of hyperthermia for the treatment of melanoma, where it synergistically increases the efficacy of chemotherapy [76]. Possible mechanisms include acceleration of apoptosis, cell necrosis without cell cycle progression, and alteration of the cell cycle [77]. The hyperthermic effect can be confined to target areas, which makes it a suitable combination with chemotherapy following cytoreduction.

Hyperthermia has been known to have a synergistic effect with some agents such as cisplatin and mitomycin C. Ratto et al. demonstrated higher tissue concentrations with hyperthermic cisplatin lavage compared with normothermic perfusion [78]. After pleurectomy or EPP, cisplatin lavage is administered into both the pleural and peritoneal cavities. An escalating dose of cisplatin (from 50-250mg/ m2) with a maximum tolerated dose of 225 mg/ m2 at 42 C has been reported to be effective. Nephrotoxicity of cisplatin can be reduced by administering sodium thiosulfate at the end of lavage procedure [79]. Richards et al. reported in a cohort of 44 patients with MPM who underwent pleurectomy followed by one hour intraoperative intracavitary hyperthermic cisplatin lavage at 42 C an overall median survival of 9 months. Intravenous sodium thiosulfate (16 g/m2 over 6 hours) was started at the end of operation to protect the kidney function. The authors reported postoperative mortality of 11% (5 of 44 patients). Major morbidity included renal toxicity (at a dose of 250 mg/m2), atrial fibrillation in 14 of 44 patients (32%), and deep venous thrombosis in 4 of 44 patients (9%). High dose (225 mg/m2) and epithelial histology were associated with favorable outcome. Twenty patients with epithelial tumors had a 26-month median survival time [<sub>80</sub>]. Intracavitary heated chemotherapy seems to be a promising approach for control of local recurrence of MPM.

# PALLIATIVE THERAPY, SUPPORTIVE CARE

Dyspnea is the most troublesome symptom of malignant mesothelioma, warranting palliative treatment. Dyspnea can be multifactorial in etiology, however, encasement of lung with tumor and recurrent pleural effusion are the most frequent causes in patients with MPM. The exudates of pleural effusion contain a large amount of protein which is secreted by both pleural layers into the pleural space. This loss of protein increases the catabolic status of patients, resulting in weight loss and diminished general well being  $[s_1]$ .

Drainage of effusions and pleurodesis can result in obliteration of the pleural space which reduces the amount of recurrent pleural effusion and improves shortness of breath. Complete drainage of the pleural effusion and reexpansion of the lung is necessary for pleurodesis and partial symptom relief. Options include thoracentesis or thoracostomy with or without chemical pleurodesis. Antibiotics, such as tetracycline, minocycline, quinacrine, and bleomycin have been used in the past. Currently, talc is the most frequently used agent. This strategy is not always successful because the effusion can become loculated during the course of the disease or as a result of repeat thoracentesis.

Insertion of a long term tunneled pleural catheter is an alternative method for controlling recurrent and symptomatic malignant effusions in patients with trapped lung and unsuccessful pleurodesis [<sub>82</sub>, <sub>83</sub>]. The Pleur-X catheters allow patients to be treated as outpatient for weeks or even months. Patients and their families can be instructed to perform home pleural drainage [<sub>84</sub>]. Pleur-X catheters should also relieve the symptoms of dyspnea and allow patients to function

independently outside of the hospital [85386387]. Further advantage of Pleur-X catheters is their cost effectiveness if placed in an ambulatory setting [88]. Relative contraindications for Pleur-X catheters include persistent dyspnea not relieved by pleurodesis and dyspnea caused by comorbidities such as congestive heart failure.

A partial pleurectomy and/or decortication might be needed to release the lung from the encasing tumor [<sub>89</sub>]. Cytoreductive pleurectomy can partially remove the tumor and improve symptoms. It can also reduce the pleural effusion and associated protein loss.

Invasion of tumor into adjacent structures causes pain [89], which results in a deterioration in quality of life. Pain management is one of the most challenging issues in MPM. Pain control can usually be achieved with narcotics. Analgesic patches such as fentanyl deliver long acting pain relief. An epidural catheter is indicated in some patients with end stage disease [12]. Radiation therapy to the hemithorax (4000-5000 cGy) sometimes helps to decrease the pain and to relieve other symptoms including superior vena cava syndrome, dysphasia, and dyspnea [90]. Palliative chemotherapy may reduce the symptoms without any significant change in the radiographic appearance of tumor. Supportive care is the only strategy for patients who refuse to undergo operation or palliative chemoradiation.

## CONCLUSION

The aggressive and diffuse nature of MPM makes a multimodality approach mandatory. At the present time, a treatment strategy including aggressive cytoreduction, extrapleural pneumonectomy or pleurectomy followed by chemoradiation is the best approach in carefully selected patients with MPM. Novel therapeutic options, such as PDT, chemotherapy, immunotherapy, gene therapy, angiogenesis inhibitors, and tumor vaccines may improve clinical outcomes and prolong mean survival. Novel targeted agents are drugs inhibiting vascular endothelial growth factor, epidermal growth factor, and platelet-derived growth factor as well as their receptors. These strategies are promising but need further investigation before they can be included in standard adjuvant regimens.

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