Malignant Pleural Mesothelioma: Medical Treatment Update

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Abstract

Malignant pleural mesothelioma (MPM) is a disease usually unaffected by current therapeutic strategies, but for the majority of patients, the use of systemic chemotherapeutic drugs remains the only therapeutic option available. During the past 15-20 years, many phase II and a few phase III clinical trials have studied a large variety of drugs such as anthracyclines, alkylating agents, platinum compounds, taxanes, vinka alkaloids, and antifolates as single agents and in combination, with the aim to increase responses and survival. The combination of pemetrexed and cisplatin tested in the largest phase III randomized trial of malignant pleural mesothelioma ever conducted has become the current standard of care. New targeted therapeutic approaches with a variety of anti–growth factor drugs are currently undergoing investigation worldwide.

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Introduction

Malignant pleural mesothelioma (MPM) is a disease usually unaffected by current therapeutic approaches. Only recently, a new combination of chemotherapy drugs has been shown to be able to induce a worthwhile benefit. The limited number of patients with MPM and their different tumor load, cell types, stages, performance status (PS), and environmental exposures seen in the clinic hamper objective evaluation of the available cytotoxic agents.

Although MPM has a slow initial growth rate, it is an aggressive malignancy that arises from mesothelial cells in the pleura. Its increasing incidence and its relationship to asbestos has attracted the attention of medical doctors (physicians, oncologists, surgeons, and pathologists) as well as epidemiologists, environmentalists, health economists, and politicians. It has a long latency period, sometimes 2 or 3 decades following exposure to asbestos. Therefore, it is difficult to predict when its incidence will reach a peak, although it is estimated that in Europe this will happen approximately in the year 2020.

History

Although asbestos has been used by humans for thousands of years, the link between its exposure and mesothelioma was first established in the Northern Cape region of South Africa during the mid 1950s.[1,2]

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Asbestos is the name given to a number of mineral fibers/rocks originally called "woolstone." There are 3 major types of asbestos fibers mined in different locations around the world: chrysotile (from the Greek words meaning "woolly" and "rock"), most frequently mined in Canada, Russia, China, and Zimbabwe; crocidolite (blue asbestos), mined in South Africa and Australia; and amosite (brown asbestos) mined almost exclusively in South Africa. The potential of these fibers to induce MPM depends on physical characteristics related to the length-to-diameter ratio of the fiber, those with the highest ratio being the most carcinogenic. Crocidolite is approximately 10 times worse than amosite, which in turn is 10 times worse than chrysotile.[3,4]

The majority of mesothelioma cases arise in people who have been directly exposed to asbestos as part of their job. It could occur in mining or in secondary industries, where it has been widely used as an insulator for heat and sound and for its good tensile strength. Mesothelioma cases occurring among people residing near but not employed in the asbestos mines and mills in the area were part of the original 1960 report of the first wave of the mesothelioma epidemic in South Africa.[1,5,6] Since that time, it has been repeatedly documented that people who reside near mines, mills, or factories that process asbestos have an increased risk of this cancer. Such occurrences have been described in relation to the large asbestos cement factory at Casale Monferrato in northwest Italy and in the vicinity of an anthophyllite mine in Finland. The Cappadocian villages of Turkey have also experienced an unprecedented epidemic, with approximately 50% of the villagers dying from mesothelioma related to erionite exposure. Erionite is present in stones that were used to

build the villages of Karain and Tuzkoy. It has a composition similar to crocidolite but has been found to be more potent than the latter in animal studies. Carbone et al demonstrated genetic predisposition to developing mesothelioma following erionite exposure. They noticed that despite the exposure to the same type of erionite, certain kindred and their descendants had a higher incidence of mesothelioma compared with other villagers. This was the first research to suggest a genetic link to mesothelioma risk.[7]

In separate studies, previous exposure to SV40, an oncogenic virus, coupled with asbestos exposure has also been shown to have a multiplicative effect on the risk of developing mesothelioma.[8]

Monitoring

Currently, response to treatment of mesothelioma is assessed by serial computed tomography scans of the chest. Traditional methods of assessing radiologic response, such as the Response Evaluation Criteria in Solid Tumors criteria, are not ideal because of the diffuse growth pattern of this cancer.[9,10]

Recently, there has been interest in molecular markers of response, such as soluble mesothelin-related peptide and osteopontin. These have been evaluated in several small cohorts, and investigations are ongoing.[11-13]

Mesothelin is a 40-kDa cell surface glycosylated phosphatidylinositol anchored glycoprotein. It is expressed by mesothelial cells and less so by healthy cells. It is overexpressed in mesothelioma, ovarian cancer, and pancreatic cancer. High levels of this marker have also been documented in high-risk patients after exposure to asbestos, predating the development of MPM. Its potential uses include screening patients at high risk of developing MPM following asbestos exposure, monitoring response to therapy, and assessing disease progression.[11,12]

Osteopontin is a glycoprotein thought to be involved in cell adhesion. It is overexpressed in lung, breast, melanoma, and colorectal malignancies.

In a small study, serum osteopontin levels were found to correlate with duration of asbestos exposure and resulting radiographic abnormalities, such as fibrosis and pleural plaques. Osteopontin levels were found to be significantly higher in patients who had pleural mesothelioma compared with those who only had asbestos exposure but no cancer.[13] Both of these markers are promising and warrant further testing in clinical trials to best determine their use and role in screening and monitoring.

Table 1A Single-Agent Chemotherapy Drugs in Malignant Pleural Mesothelioma

Study	Drug	Number of Patients	Response Rate, %
	Anthracycline Derivatives		
Lerner et al[19] Sorensen el al[20]	Doxorubicin	66	11
Kaukel et al[21]	Pirarubicin	35	22
Colbert et al[22]	Detorubicin	35	26
Magri et al[23] Mattson et al[24]	Epirubicin	59	14
Oh et al[25] Baas et al[26] Hillerdal et al[27]	Liposomal doxorubicin	109	5
Steele et al[28]	Liposomal daunorubicin	14	0
Eisenhauer et al[29] Van Breukelen et al[30]	Mitoxantrone	62	5
	Alkylating Agents		
Sorensen et al[20]	Cyclophosphamide	16	0
Falkson et al[31]	Amsacrine	36	6
Alberts et al[32] Zidar et al[33] Falkson et al[34]	Ifosfamide	83	7
Bajorin et al[35]	Mitomycin C	19	21
	Platinum Derivatives		
Zidar et al[36] Mintzer et al[37] Planting et al[38]	Cisplatin	73	18
Vogelzang et al[39] Mbidde et al[40] Raghavan et al[41]	Carboplatin	89	11
	Antimetabolites		
Solheim et al[42]	Methotrexate	60	37
Kindler et al[43]	Edatrexate	20	25
Scagliotti et al[44]	Pemetrexed	64	9
Vogelzang et al[45]	Trimetrexate	52	12
Harvey et al[46]	5-Fluorouracil	20	5
Kindler et al[47] Van Meerbeeck et al[48] Bischoff et al[49]	Gemcitabine	60	12

Resectable Mesothelioma

Patients who can safely undergo optimal cytoreductive surgery without leaving gross disease at completion are considered candidates for surgical management.

The optimal surgical approach has not been clarified. Ultimately, the decision regarding the most appropriate surgical procedure is guided by multiple variables, including PS, stage of the disease, comorbid diseases, and respiratory reserve.

Pleurectomy is most useful in palliating recurrent pleural effusions and thus improving respiratory symptoms. In experienced centers, the complication rate is fairly low, with the main complications being prolonged air leak, pneumonia, empyema, and respiratory insufficiency.[14]

Extrapleural pneumonectomy (EPP) is a more radical surgery involving removal of the ipsilateral lung along with visceral and parietal pleura, pericardium, phrenic nerve, and part of the diaphragm. Because of high perioperative morbidity, patients must be carefully selected for this procedure. Major complications arising from this procedure are atrial fibrillation and broncho-pleural fistulae. The number of patients undergoing EPP has been limited by the level of technical expertise required for successful surgery and the highly selected group of patients who are candidates.[15]

The role and impact of multimodality treatment incorporating neoadjuvant chemotherapy, EPP, and adjuvant radiation needs further elucidation through ongoing clinical trials.

Table 1B Single-Agent Chemotherapy Drugs in Malignant Pleural Mesothelioma

Study	Drug	Number of Patients	Response Rate, %
	Camptothecins		
Falkson et al[50]	Acivicin	40	0
Kindler et al[51]	Irinotecan	28	0
Maksymiuk et al[52]	Topotecan	22	0
	Taxanes		
Vogelzang et al[53] Van Meerbeeck et al[54]	Paclitaxel	60	5
Belani et al[55] Vorobiof et al[56]	Docetaxel	51	7.5
	Vinca Alkaloids		
Martensson et al[57]	Vincristine	23	0
Cowan et al[58]	Vinblastine	20	0
Kelsen et al[59] Boutin et al[60]	Vindesine	38	3
Steele et al[61]	Vinorelbine	29	24
Talbot et al[62]	Vinflunine	67 (62*)	13.8
	Epipodophyllotoxins		
Sahmoud et al[63] Tammilehto et al[64]	Etoposide	111	3
	Novel Compounds		
Giaccone et al[65]	ZD0473	41	0
Mikulski et al[66]	Ranpirnase	105	5
Vogelzang et al[67] Dhingra et al[68]	DHAC	56	13
Janne et al[69]	Sorafenib	51 (43*)	4.7
Garland et al[70]	Erlotinib	63 (33*)	0
Govindan et al[71]	Gefitinib	43	4
Jahan et al[72]	Vatalanib	47 (46*)	11

*Patients with measurable disease who were assessed for response.

Systemic Medical Therapies

Before systemic therapy is considered, it is very important to evaluate other prognostic factors strongly associated with MPM, such as advanced age and comorbidities, which in many instances, preclude the use of any available therapeutic approach.[16,17]

However, systemic therapy remains the only option for the majority of patients with MPM. There are a few cytotoxic drugs that can induce a benefit in the form of a sustained response, albeit in a small number of patients. The large majority of published studies, in full or abstract form, have been phase II trials. Unfortunately, many of them have flaws in their designs, with different pathologic variants treated and with response measurements not always reported or standardized.[18]

Single-Agent Therapy

As single agents, a wide variety of drugs have been tested in MPM. Comprehensive lists of agents have been published and updated in the past 10 years. These lists include different family compounds, such as anthracyclines and anthracenediones (doxorubicin, epirubicin, mitoxantrone, pirarubicin, detorubicin, liposomal encapsulated doxorubicin); alkylating agents (cyclophosphamide, ifosfamide, mitomycin C); platinum compounds (cisplatin, carboplatin, oxaliplatin), vinka alkaloids (vincristine, vinorelbine, vindesine, vinflunine); taxanes (paclitaxel, docetaxel); antimetabolites (5-fluorouracil, methotrexate, gemcitabine, 5-azacytidine, edatrexate, pemetrexed, trimetrexate); other drugs, such as amsacrine and topotecan; and biologics (BCG, interferon α, β and γ; and interleukin-2).

Some of these drugs are capable of exerting overall response rates (ORRs) of 10%-30%, but because of the different numbers of patients treated in different trials and institutions, the percentage of response varies substantially (Table 1).[19-72]

With the emerging role of biologic agents in the treatment of solid tumors and hematologic diseases, many phase II trials took place in the 1980s and 1990s in an attempt to modulate the immune response. These cytokines (interferons, interleukins) were used both systemically and intrapleurally, with limited RRs. Because MPM expresses vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), targeted agents with a variety of drugs aimed at these and other angiogenic growth factors have been under investigation.

Sorafenib, a multitargeted tyrosine kinase inhibitor (TK; TKI) of VEGF, PDGF, and Raf, was evaluated in a single-arm phase II trial, the primary endpoint of which was RR, in both pretreated and chemotherapy-naive patients. Response rates were quite disappointing (4.7%); thus, the trial failed to reach its primary endpoint.[69]

Recently reported phase II trials of erlotinib and gefitinib by the Southwest Oncology Group and Cancer and Leukemia Group B (CALGB) failed to show any activity of these drugs in MPM.[70,71]

Dasatanib, histone deacytelase inhibitors, and proteasome inhibitors are also the subjects of ongoing phase II clinical trials.

Vatalanib is known to inhibit both VEGF and PDGF receptor TKs. A phase II CALGB trial in 47 eligible (46 evaluable) chemotherapy-naive patients was conducted. The primary endpoint of the study was a 3-month progression-free survival (PFS) rate of 75%. Although this was not achieved, a moderate response of 11% (partial responses [PRs]) and a median survival of 10 months (similar to other previously reported single agents) were documented.[72]

Chemotherapy can also be administered locally into the pleura. Intrapleural infiltration or instillation of chemotherapy have been attempted through an intracavitary chest tube or as part of complex surgical protocols (as adjuvant to surgery).

Combination Chemotherapy

The majority of clinical trials have used combinations of drugs that have shown some activity when administered as single agents. The purpose is to combine more effective drugs but with different toxicity profiles. Most of the combinations in prospective phase II trials and in some randomized phase III trials have focused on the combined use of anthracyclines (epirubicin and doxorubicin) with platinum compounds (cisplatin and carboplatin) and, for the past few years, with gemcitabine.[73-103]

This last combination (cisplatin/carboplatin plus gemcitabine), which is widely used in non–small-cell lung cancer, has been ex-

tensively tested in Australia and rapidly became popular in many oncology centers despite the fact that the responses documented were similar to other tried combinations. The toxic effects were somewhat diminished, making it an attractive therapy.[91]

Combination chemotherapy does not appear to yield higher RRs or longer duration of responses than single agents. The most common combinations reported in the 1990s were platinum and anthracycline compounds or gemcitabine (Table 2).[73-105]

The results of a large, randomized clinical trial comparing cisplatin alone with cisplatin plus pemetrexed, an antifolate, were presented at the 2002 plenary session of the American Society of Clinical Oncology meeting and published in July 2003. This was the largest-ever prospective, randomized, international clinical trial performed in MPM. It was well planned, and the measuring of tumor responses was meticulous. The documented results confirmed that a combination of chemotherapy (in this instance, cisplatin plus pemetrexed) is an effective treatment, and it rapidly became the new standard of care, superseding the use of single agents and other previously reported combinations.[96]

A number of phase II trials have been published in the past few years, mainly in abstract form. From Italy, a combination of pemetrexed plus carboplatin was tested in 76 patients and showed a moderate ORR of 24% (including 3 complete responses) with moderate side effects, although hematologic grade 3/4 was present in > 50% of the patients.[98]

In a smaller study of 10 patients with a mixed variety of characteristics such as previous chemotherapy, pleural and peritoneal sites, and different histologic subtypes, the combination of oxaliplatin plus gemcitabine did not induce responses, although 4 patients had disease stabilization.[99]

A combination of liposomal doxorubicin, gemcitabine, and carboplatin was administered to 167 patients, and a RR of 33% was documented in a phase II study by the Nordic mesothelioma groups. This study was conducted before cisplatin plus pemetrexed became the standard of care. Although 23% of patients stopped therapy as a result of hematologic toxicity, 12-month survival was encouraging at 50%.[100]

The European Organization for Research and Treatment of Cancer and the NCI-C conducted a trial comparing raltitrexed plus cisplatin with cisplatin alone. A median survival of 11 months versus 8.8 months, favoring the combination arm was measured; however, it failed to reach statistical significance.[101]

Bevacizumab, a monoclonal antibody (MoAb) toward VEGF, has also been the subject of clinical studies. Bevacizumab in combination with cisplatin and gemcitabine compared with the latter chemotherapy alone, showed fairly similar results, with PFS times of 6.9 months and 6 months for the bevacizumab containing and placebo arms, respectively.[102]

Other clinical trials assessing the efficacy of bevacizumab in addition to pemetrexed/cisplatin or carboplatin are under way.

The combination of pemetrexed plus gemcitabine was prospectively tested in a randomized phase II clinical trial and recently published.[103] The RR documented was 26% and 17% in 2 cohorts who received the same drugs but in 2 different regimens. The response was somehow lower than that experienced with cisplatin and pemetrexed and with an inferior survival. Furthermore, the gemcitabine plus pemetrexed combination induced a higher rate of grade 3/4 hematologic toxicities.

There is no established standard of care for second-line therapy. Single-agent pemetrexed has shown activity (PR rate of 21%) in second-line treatment in patients not previously exposed to this agent.[104]

Table 2 Combination Chemotherapy in Malignant Pleural Mesothelioma

Study	Drug	Number Of Patients	Response Rate, %
Samson et al[73]	Doxorubicin + Cyclophosphamide	36	11
Samson et al[73] Dhingra et al[74]	Doxorubicin + Cyclophosphamide + DTIC	60	17
Carmichael et al[75] Dirix et al[76]	Doxorubicin + Ifosfamide	40	23
Ardizzoni et al[77] Chahinian et al[78]	Doxorubicin + Cisplatin	59	19
Shin et al[79]	Doxorubicin + Cisplatin + Cyclophosphamide	23	30
Chahinian et al[80]	Doxorubicin + 5-Azacytidine	36	22
Upham et al[81]	Doxorubicin + Interferon-α	24	16
Pennuci et al[82]	Doxorubicin + Cisplatin + Mitomycin	24	21
Breau et al[83]	Doxorubicin + Cisplatin + Bleomycin + Mitomycin	25	44
Magri et al[84]	Epirubicin + Ifosfamide	17	6
Zidar et al[85]	Rubidazone + DTIC	23	0
Koschel et al[86]	Pirarubicin + Cisplatin	39	15
Samuels et al[87]	Cisplatin + DHAC	36	17
Tsavaris et al[88]	Cisplatin + Vinblastine	20	25
Chahinian et al[78]	Cisplatin + Mitomycin	35	26
Tansan et al[89]	Cisplatin + Mitomycin + Interferon-α	20	11
Soulie et al[90]	Cisplatin + Interferon-α	26	38
Byrne et al[91] Van Haast et al[92] Kindler et al[93] Nowak et al[94]	Cisplatin + Gemcitabine	92	16-48
Aversa et al[95]	Carboplatin + Gemcitabine	20	20
Vogelzang et al[96]	Cisplatin + Pemetrexed	226	41
Fizazi et al[97]	Raltitrexed + Oxaliplatin	70	20
Castagneto et al[98]	Carboplatin + Pemetrexed	76	24
Boyar et al[99]	Oxaliplatin + Gemcitabine	10	0
Hillerdal et al[100]	Liposomal Doxorubicin + Gemcitabine + Carboplatin	167	33
Van Meerbeeck et al[101]	Cisplatin + Raltitrexed	250 (213*)	23.6
Karrison et al[102]	Bevacizumab + Gemcitabine + Cisplatin	115 (108*)	25
Janne et al[103]	Pemetrexed + Gemcitabine	56	26
Sorenson et al[104]	Pemetrexed + Gemcitabine	52	17
Zucali et al[105]	Gemcitabine + Vinorelbine	28 (26*)	7.4

*Patients with measurable disease who were assessed for response.

In patients pretreated with pemetrexed, the combination of gemcitabine and vinorelbine is well tolerated and can be offered as palliation.[105]

Conclusion

Significant progress has been made over the years in an attempt to increase treatment options for patients afflicted with MPM. Perhaps the most exciting advance has been the establishment of pemetrexed plus cisplatin as the standard of care for first-line treatment of advanced disease. This combination was found to offer both a survival and quality-of-life benefit. For patients with localized disease, surgery is the mainstay of therapy, predominantly aimed at cytoreduction and palliation of symptoms. The role of neoadjuvant chemotherapy needs to be prospectively evaluated, as does the use of multimodality therapy incorporating surgery, chemotherapy, and radiation.

The therapeutic value of VEGF inhibition by MoAbs and small-molecule TKIs is currently the subject of clinical studies. Targeting the epidermal growth factor receptor pathway has also been investigated, with guarded results.

There is currently no standard of care for second-line therapy. Numerous studies have evaluated drugs like vinca alkaloid derivatives (vinflunine and vinorelbine), with some encouraging results.

The emergence of osteopontin and mesothelin-related peptide as potential screening tools might assist in identifying high-risk patients with genetic susceptibility following asbestos exposure early in the course of the disease. However, further studies are required to clearly define their role in clinical practice.

A myriad of questions remain unanswered, underpinning the need for ongoing research in an effort to improve the outcomes of patients afflicted by this otherwise resistant disease.

Disclosures

The authors have no relevant relationships to disclose.

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