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Evidence-based Series #7-14-1: Section 1

The Use of Chemotherapy in Patients with Advanced Malignant Pleural Mesothelioma: A Clinical Practice Guideline

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A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: October 18, 2005

Questions

1. In patients with advanced malignant pleural mesothelioma, does palliative chemotherapy improve quality of life or symptom control?
2. In patients with advanced malignant pleural mesothelioma, does palliative chemotherapy improve survival?
3. Which chemotherapeutic agents (or combinations of agents) have shown the highest response rates?

Target Population

The recommendations apply to adult patients with advanced, symptomatic malignant pleural mesothelioma who have a good performance status (Eastern Cooperative Oncology Group 0-1) and are not suitable for surgical resection.

Recommendations and Key Evidence

Despite many reports on the use of chemotherapy in the palliative treatment of malignant pleural mesothelioma, only a limited amount of high-quality evidence exists on which to base recommendations. Based on this limited evidence, the Lung Cancer Disease Site Group offers the following opinions:

- **Pemetrexed 500 mg/m² and cisplatin 75 mg/m² every 3 weeks, with vitamin supplementation with B₁₂ 1000 µg monthly and folic acid 0.4-1.0 mg daily is recommended for the palliative treatment of adult patients with advanced malignant pleural mesothelioma. Both vitamin supplements should be started before the administration of pemetrexed.**
- **If pemetrexed is not available, there is evidence from a smaller trial (n=250) to recommend the use of raltitrexed 3 mg/m² and cisplatin 80 mg/m² every three weeks. This trial found a significant survival difference (p=0.0483) and the hazard ratio for the raltitrexed trial was very similar to that of the pemetrexed trial (HR 0.76 versus HR 0.77, respectively). However, response rate and progression-free survival did not achieve conventional statistical significance in the raltitrexed trial.**

Key Evidence

- One large randomized trial comparing chemotherapy with pemetrexed 500 mg/m² and cisplatin 75 mg/m² every three weeks to cisplatin alone demonstrated improved survival and quality of life for the two-drug combination versus single-agent cisplatin. That trial included 448 eligible patients randomized to either single-agent cisplatin or the combination regimen. Response rates (41% versus 17% respectively, p<0.001), time to progression (5.7 versus 3.9 months, p=0.001), and survival (12.1 versus 9.3 months, hazard ratio 0.77, p=0.020) all favoured combination treatment. Grades 3 and 4 toxicity were higher with the combined treatment: neutropenia (28% versus 2%), thrombocytopenia (6% versus 0%), vomiting (13% versus 4%), and febrile neutropenia (2% versus 0%). Two quality-of-life indices (dyspnea and pain) assessed using the Lung Cancer Symptom Scale were significantly improved with pemetrexed and cisplatin after six cycles of treatment (p=0.004 and p=0.017, respectively).
 - A second trial randomised 250 patients to either raltitrexed plus cisplatin, versus cisplatin alone. This trial demonstrated a significant improvement in survival (11.4 versus 8.8 months, HR=0.76, p=0.0483). This trial also showed a higher response rate (23.6% versus 13.6%, p=0.056) and longer progression free survival (5.3 versus 4 months, HR=0.78, p=0.058), although these differences did not achieve conventional statistical significance.
 - Currently there is no direct evidence to support or refute whether chemotherapy extends survival or improves quality of life as there are no trials comparing chemotherapy to best supportive care. However, the opinion of the Lung Cancer Disease Site Group is that single-agent cisplatin, the control arm for both the randomized trials, is unlikely to reduce survival in this patient population. Thus, the opinion of the Lung Cancer Disease Site Group is that the above trials provide sufficient indirect evidence that pemetrexed and cisplatin combination chemotherapy will improve survival and quality of life for these patients, and is therefore, recommended.
 - One hundred eleven noncomparative phase II trials were identified that examined chemotherapy for patients with malignant pleural mesothelioma. The pooled response rates for trials examining platinum-containing regimens as single agents (14.3%, 9 trials) or in combination with other agents (24.9%, 19 trials) are higher than the pooled response rates for trials examining non-platinum-containing regimens as single agents (3.6% to 9.0%, 51 trials) or in combination (10.4%, 12 trials).
- **The routine substitution of carboplatin for cisplatin is not recommended.**

Key Evidence

- Data from eight noncomparative phase II trials indicate that the pooled response rates to single-agent carboplatin are less than cisplatin (10.1% versus 20.0%).
- **Given the limited amount of high-quality evidence on the role of chemotherapy in malignant pleural mesothelioma, patients should be encouraged to participate in clinical trials of treatment for this disease.**

Key Evidence

- The participation of this group of patients in clinical trials is important as the absence of adequately powered clinical trials has contributed to the limited evidence about treatment benefits for malignant pleural mesothelioma to date.

Related Guidelines

- Evidence Summary Report #7-14-2: *Surgical Management of Malignant Pleural Mesothelioma.*
- Evidence Summary Report #7-14-3: *The Role of Radiation Therapy in Malignant Mesothelioma of the Pleura*

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Evidence-based Series #7-14-1: Section 2

The Use of Chemotherapy in Patients with Advanced Malignant Pleural Mesothelioma: A Systematic Review

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A Quality Initiative of the
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Report Date: October 18, 2005

QUESTIONS

1. In patients with advanced malignant pleural mesothelioma (MPM), does palliative chemotherapy improve quality of life (QOL) or symptom control?
2. In patients with advanced MPM, does palliative chemotherapy improve survival?
3. Which chemotherapeutic agents (or combinations of agents) have shown the highest response rates?

INTRODUCTION

Patients with MPM generally present with symptomatic advanced disease. Until recently, there was no standard palliative systemic therapy. The prognosis for these patients is poor, with several early retrospective studies reporting five-year survivals of 1% or less (1-3) and overall median survivals equal to or less than 7.6 months (1-4) for patients not receiving chemotherapy. QOL can be significantly affected by pain, shortness of breath, cough, and weight loss, and chemotherapy may offer palliation of symptoms and improvements in both QOL and survival.

MPM is an aggressive neoplasm that arises in the pleura. The unique growth pattern of MPM makes it difficult to assess tumor response to treatment. Malignant mesotheliomas often grow as a "rind" around the pleural surface, which may not produce spherical lesions with bidimensional measurements (5). Different criteria have been used for tumour assessment in mesothelioma; however, there is variability between these criteria. For example the WHO criteria (6) were developed to assess bidimensionally measurable disease whereas the RECIST criteria (7) are more suited to unidimensional measurements.

The provincial Lung Cancer Disease Site Group (Lung DSG) identified a need to summarize the available evidence supporting the use of chemotherapy for MPM. This systematic review address the following questions: 1) Does chemotherapy improve survival, QOL, or symptom control, compared to best supportive care (BSC)? 2) Which chemotherapeutic agents (or combinations of agents) have shown the highest response rates in patients with advanced MPM? Guidelines addressing the role of surgery and radiation in patients with MPM have also been developed (see "Related Evidence Summaries" section)

METHODS

This practice guideline was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (8). Evidence was selected and reviewed by two members of the PEBC's Lung DSG and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on the use of chemotherapy in patients with MPM. The body of evidence in this review is primarily comprised of mature randomized controlled trial data. That evidence forms the basis of a clinical practice guideline developed by the Lung DSG. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

Evidence was identified through a systematic search of MEDLINE (1966 through October 2005), EMBASE (1980 through October 2005), CANCERLIT (1966 to March 2002), and the Cochrane Library databases (2005, Issue 3). Search terms used included "mesothelioma", (Medical subject heading (MeSH) and Excerpta Medica Tree (EMTREE) term) with and without the subheading "drug therapy", combined with "drug therapy" (MeSH), "chemotherapy, adjuvant" (MeSH), and "antineoplastic agents" (MeSH), "chemotherapy" (EMTREE), "adjuvant therapy" (EMTREE), and the text word "mesothelioma". Those terms were combined with the search terms for the following study designs and publication types: practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, phase II or III clinical trials, and multicenter or comparative studies.

In addition, conference proceedings of the American Society of Clinical Oncology (ASCO) for the years 1997-2005 were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guidelines Clearinghouse (<http://www.guideline.gov/index.asp>) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Inclusion Criteria

Articles published as full reports or as abstracts were selected for inclusion in this systematic review of the evidence if they were:

1. Practice guidelines, systematic reviews, or meta-analyses evaluating the use of chemotherapy for MPM.
2. Randomized clinical trials (RCTs) comparing chemotherapy with BSC, or different chemotherapy regimens.
3. Phase II clinical trials evaluating chemotherapy, either as single agents or combinations of agents.
4. Phase II clinical trials evaluating chemotherapy (single-agent or in combination) combined with immunotherapies such as interferon and interleukin, and if they met the following criteria:
5. Study population included patients with MPM. Studies including patients with both pleural and peritoneal malignant mesothelioma were also eligible.
6. Outcomes of response, survival, QOL, or symptom control were reported.

Exclusion Criteria

The following were excluded from the systematic review:

1. Papers published in a language other than English.
2. Clinical trials primarily assessing immunotherapies.
3. Trials of chemotherapy combined with surgery and/or radiation therapy.

The literature search for phase II trials was not updated after April 2002 as there were data from large randomized trials on which to make treatment recommendations.

Synthesizing the Evidence

As the chemotherapy regimens involved were heterogeneous, the results of the randomized trials were not pooled. A decision was made to group the phase II trials according to the following major categories: single-agent chemotherapy, non-platinum combinations, single-agent platinum agents, combination platinum agents, and chemotherapy plus immunotherapy. The response rates of the noncomparative trials were pooled by the formula $PRR = \sum(w_i RR_i) / \sum w_i$, where PRR is the pooled response rate of the studies, w_i is the weight of the i^{th} study, and RR_i is the response rate of the i^{th} study (9). RR was calculated by dividing the proportion of complete or partial responses by the total number of patients in a study. 'w' was determined by the inverse of the variance for a study, with the variance calculated by multiplying the proportion of patients with a complete or partial response with the proportion of patients with no response and then dividing the result by the total number of patients in the study. The 95% confidence interval (95% CI) for each PRR was calculated by the formula $PRR \pm 1.96SE_{PRR}$, where $SE_{PRR} = \sqrt{1/\sum w_i}$ (9).

RESULTS

Literature Search Results

The results of the literature search are summarized in Table 1. Of the relevant studies retrieved eight were randomized trials (10-17) and the remainder were non-comparative studies: 55 regimens (reported in 52 papers) focused on non-platinum-based single-agent chemotherapy (18-69), 12 researched non-platinum-based combination chemotherapy (70-81), 35 concentrated on platinum-based chemotherapy (82-116), and 12 investigated chemotherapy and immunotherapy (117-128). No evidence-based clinical practice guidelines for the treatment of mesothelioma were identified, although in 2001 the British Thoracic Society (BTS) published a statement intended to guide the management of malignant mesothelioma (129). The statement was developed through a review of literature and expert consensus; however, a comprehensive and systematic review of the literature was not attempted, and the BTS indicated that limitations on the quality of evidence did not allow for the development of recommendations.

A systematic review by Berghmans et al (130) was published in 2002 that reviewed the activity of chemotherapy and immunotherapy on malignant mesothelioma. The review included both pleural and peritoneal malignant mesotheliomas and included searches of the databases of MEDLINE, HEALTH STAR, and the National Cancer Institute. The extent of the literature search is not known because a search strategy was not provided by the authors. The review identified 83 articles for inclusion, and the authors divided the trials into the following four groups: cisplatin regimens without doxorubicin, doxorubicin regimens without cisplatin, regimens containing both cisplatin and doxorubicin, and, finally, regimens not containing cisplatin or doxorubicin. The current systematic review has identified more trials than the review by Berghmans et al (130), even though the inclusion and exclusion criteria were very similar. Also, the current systematic review has grouped the trials into their respective drug types, allowing for a more organized investigation into the action of different drug types on MPM.

There were no RCTs of chemotherapy versus BSC. Two large randomized trials comparing single-agent cisplatin with a cisplatin combination were identified. The six remaining randomized trials that compared chemotherapy regimens were generally small to medium sized and underpowered. Data from all these trials are included.

The majority of trials identified in the literature search that evaluated systemic therapy for MPM were non-comparative phase II clinical trials. Data from these 111 trials have been organized into meaningful subgroups, based on the type of chemotherapy, to allow an exploratory comparison of response rates between different chemotherapy agents.

Table 1. Summary of trials selected for inclusion in this evidence summary report.

Study Type / Regimen	Number of published studies	Number of published abstracts	Reference numbers	Relevant Table
Randomized trials	8	0	(10-17)	Table 2
Noncomparative studies non-platinum-based, single-agent chemotherapy				
Temozolomide, Ifosfamide, or cyclophosphamide	7	0	(18-24)	Appendix 1, Table A1
Anthracyclines, liposomal anthracyclines or mitoxantrone	10	0	(25-34)	Appendix 1, Table A2
Taxanes	3	1	(35-38)	Appendix 1, Table A3
Vinca alkaloids	5	0	(39-43)	Appendix 1, Table A4
Gemcitabine	2	1	(44-46)	Appendix 1, Table A5
Antimetabolites	7	1	(34,47-53)	Appendix 1, Table A6
Topoisomerase inhibitors	3	1	(54-57)	Appendix 1, Table A7
Experimental agents	9	3	(58-69)	Appendix 1, Table A8
Noncomparative studies: non-platinum-based, combination chemotherapy				
	8	4	(70-81)	Appendix 1, Table A9
Noncomparative studies: platinum-based chemotherapy				
Single agent	9	0	(82-90)	Appendix 1, Table A10
Combination regimens	19	7	(91-116)	Appendix 1, Table A11
Noncomparative studies with chemotherapy and immunotherapy				
	12	0	(117-128)	Appendix 1, Table A12
TOTAL	101 ^a	18		

^a One non-comparative study (33) had two arms of two different drug class regimens, and is counted as one study in the total

Outcomes

The studies in this report exhibited wide variability in their patient inclusion and exclusion criteria. Almost all the studies included patients with performance status 0-2. Many studies allowed the inclusion of patients who had received prior chemotherapy. Some studies included patients with measurable or evaluable disease, whereas others included only patients with measurable disease. Additionally, the criteria used to assess response differed across trials, with most trials using the WHO criteria (bidimensional measurements), and more recent studies using the RECIST and modified RECIST criteria. Most studies did not have a central panel review of pathology and there was considerable variation between studies in the time from diagnosis and chemotherapy administration. The QOL measures used also varied between studies. Many trials included only patients with MPM, whereas others also included small numbers of patients with peritoneal mesothelioma. These differences make statistical comparisons between individual studies inappropriate. Accordingly, the data have been

organized by grouping together similar study types in order to provide aggregate data on response rates where possible. A determination of the factors that are predictive for those patients more likely to respond to treatment was considered beyond the scope of this review.

Randomized Trials

No randomized clinical trials comparing chemotherapy to BSC were found. Eight published randomized clinical trials ranging in size from 16 to 456 patients were identified (10-17) (see Table 2). Seven of these studies compared different chemotherapy regimens, while the eighth study randomized patients to receive or not receive an immunomodulator in addition to chemotherapy (12).

In one large randomized study, Vogelzang et al treated 448 eligible patients with either pemetrexed and cisplatin or cisplatin alone (11). 118 patients signed informed consent but were not randomized. The reasons for excluding these patients are unclear and this could limit the generalizability of the results. The trial design was modified, after 70 patients were enrolled, to allow all patients to receive vitamin supplements because of concerns about excess toxicity in the combination arm. Patients received vitamin B₁₂ (1000 µg every nine weeks) and folic acid (350-1000 µg daily) supplementation commencing at least one week prior to chemotherapy. The original sample size was increased to compensate for that modification. Response rates (41% versus [vs] 17%, $p < 0.001$), time to progression (5.7 vs 3.9 months, $p = 0.001$), and survival (median, 12.1 vs 9.3 months; hazard ratio [HR] 0.77, $p = 0.020$) all favored the combination. Vitamin supplementation did not appear to reduce any of the efficacy outcomes. Grade 3 or 4 toxicities were significantly more frequent in the combined treatment arm for all hematological toxicities and nausea, vomiting, diarrhea, dehydration and stomatitis. There were fewer drug-related deaths in the cisplatin arm compared to the combination arm (4% vs 6%). Patients who received the fully supplemented regimen experienced lower rates of hematological toxicity (grade 3 or 4 neutropenia, 23% vs 41%, $p = 0.011$ or febrile neutropenia, 1% vs 5%, $p = 0.053$, leukopenia 15% vs 26%, $p = 0.72$) and vomiting (11% vs 21%, $p = 0.071$) than those who received partial or no supplementation. The Lung Cancer Symptom Scale was used to assess QOL and data were presented at the ASCO meeting in 2002. Dyspnea and pain were significantly improved for patients receiving pemetrexed and cisplatin after six cycles of treatment ($p = 0.004$ and $p = 0.017$), respectively (131,132).

In another large phase III trial reported by Van Meerbeeck et al (10), 250 patients were randomized to receive either raltitrexed and cisplatin or cisplatin alone. The median number of cycles of raltitrexed/cisplatin administered was five (range 1-10). Median survival was 11.4 for the combination versus 8.8 months for single-agent cisplatin (HR = 0.76, $p = 0.0483$). Overall response rates (24% vs 14%, $p = 0.056$) and progression free survival (5.3 vs 4.0 months, HR = 0.78, $p = 0.058$) were greater in the combination treatment arm, but neither difference achieved conventional statistical significance. More patients in the combination group developed neutropenia (16% vs 8%), fatigue (12% vs 6%), nausea (14% vs 10%), and vomiting (13% vs 7%). There was no statistically significant difference in global QOL between the two groups (details of data not provided).

Samson et al (15) randomized 96 patients to receive chemotherapy with cyclophosphamide, doxorubicin, and imidazole carboxamide or cyclophosphamide and doxorubicin alone. There were no significant differences in response rate (13% vs 11%), median time to disease progression (2.1 months vs 3.2 months), or median survival (5.5 months vs 6.7 months) respectively. Chahinian et al (14) randomized 79 patients to cisplatin with either mitomycin or doxorubicin. The response rate for cisplatin–mitomycin was greater than that for the doxorubicin–cisplatin combination (26% vs 14%). Median time to treatment failure (3.6 vs 4.8 months, respectively, $p = 0.59$) and median survival (7.7 vs 8.8 months, $p = 0.75$) were similar between the two treatment groups.

Table 2. Randomized trials comparing different types of chemotherapy.

Ref.	Inclusion criteria	Intervention	Number of patients	Histology: Epi/ Sar/ Mixed/ Other	Response: CR / PR / SD (RR, 95% CI)	PFS/TTP Median (mo)	Survival Median (mo)
Van Meerbeeck et al, 2005 (10)	MPM, no prior CT, PS ≤ 2, adequate hematological, renal, and hepatic function	Ral 3 mg/m ² + Cis 80 mg/m ² , both d1 q3wk	126	94 /18 /5 /9	2 / 24 / 58 ^a (24%, 16%-32%)	5.3 (PFS)	11.4
		Cis 80mg/m ² d1 q3wk	124 (Total: 250 entered & evaluated)	75 /30 /8 /11	0 / 14 / 56 ^a (14%, 7%-20%) p=0.056 χ^2	4.0 (PFS) (HR = 0.78, p=0.058 logrank)	8.8 (HR=0.76, p=0.0483 logrank)
Vogelzang et al, 2003 (11)	MPM, uni- or bidimensionally measurable disease, KPS ≥ 70, no prior CT	Pem 500mg/m ² + Cis 75mg/m ² , both d1 q3w	226	154/18/37/17	NR (41%, 35%-48%)	5.7 (TTP)	12.1
		Cis 75mg/m ² d1 q3wk	222 (Total: 456 entered 448 evaluated)	152/25/36/9	NR (17%, 12%-22%) p<0.001	3.9 (TTP) (HR=0.68, p=0.001 logrank)	9.3 (HR=0.77, p=0.020 logrank)
O'Brien et al, 2000 (12)	NSCLC and MM, PS 0-2, measurable or evaluable disease	Cis 50mg/m ² + Vb 6mg/m ² + Mit 8mg/m ² q3wk	5	NR	PR 1 (of 5 pts)	NR	NR
		Cis + Vb + Mit as above + SRL172 Monthly	4 (Total: 29 entered, 9 with MM)	NR	PR 2 (of 4 pts)	NR	NR
White et al, 2000 (13)	NSCLC and MM, KPS ≥50	Cis 80mg/m ² d1+ Etop 120mg/m ² d1-3	13	NR	0 / 1 / 4 (8%)	NR	4.3 ^b
		Cb 100mg/m ² /wk	12 (Total:120 entered, 25 with MM)	NR	0 / 0 / 7 (0%)	NR	5.0 ^b p=0.0135
Chahinian et al, 1993 (14)	MM, measurable or assessable, PS 0-2, no prior CT, prior RT allowed	Cis 75mg/m ² + Mit 10mg/m ² q4wk	35	24 / 0 / 0 / 11 ^c	2 / 7 ^d /15 (26%, 12%-43%)	3.6 (TTF)	7.7
		Cis 75mg/m ² + Dx 60mg/m ² q4wk	35 (Total: 79 entered, 70 evaluated)	24 / 0 / 0 / 11 ^c	0 / 5 ^d / 15 (14%, 5%-30%)	4.8 (TTF) p=0.59 logrank	8.8 p=0.75 logrank
Samson et al, 1987 (15)	MM stage II, III or IV, no prior CT, prior RT allowed, measurable or evaluable disease, PS 0-3	Cy 500 mg/m ² + Dx 50mg/m ² d1 q3wk	36	16 / 6 / 7 / 7	NR (11%)	3.2 ^a (Relapse-free)	6.7 ^{b,e}
		Cy + Dx as above + IC 250 mg/m ² d1-5	40 (Total: 96 entered, 76 evaluated)	21 / 3 / 5 / 11	NR (13%)	2.1 ^a (Relapse-free) p=NS	5.5 ^{b,e} p=NS
Cantwell et al, 1986 (16)	MPM, measurable or assessable disease, prior CT allowed, PS 0-3	Cb: 400mg/m ² monthly	9	NR	0 / 2 / 2 (22%, 2.8%-60%)	NR	NR
		JM9: 300mg/m ² monthly	7	NR	0 / 0 / NR (0%)	NR	NR
Sorensen et al, 1985 (17)	MM, unresectable, measurable disease, PS 0-2	Dx 60mg/m ² q3wk	15	Overall: 9 / 7 / 16 / 0	0 / 0 / 0 (0%)	NR	NR
		Cy 1500mg/m ² q3wk All pts received the alternate drug at disease progression	16 (Total: 32 entered, 30 evaluated)		0 / 0 / 0 (0%) All pts PD	NR	NR

Notes: Cb – carboplatin, CI – confidence interval, Cis – cisplatin, CR – complete response, CT – chemotherapy, Cy – cyclophosphamide, d – day, Dx – doxorubicin, Etop – etoposide, Epi – epithelial, HR – hazard ratio, IC – imidazole carboxamide, JM9 – platinum analogue, KPS – Karnofsky performance status, Mit – mitomycin, MM – malignant mesothelioma (pleural or peritoneal), MPM – malignant pleural mesothelioma, NR – not reported, NS – not significant, NSCLC – non-small cell lung cancer, PD – progressive disease, PFS – progression-free survival, PR – partial response, PS – performance status, Pem – pemetrexed, pts – patients, q – every, Ral – raltitrexed, Ref. – reference, RR – response rate, RT – radiotherapy, Sar – sarcomatous, SD – stable disease, SRL172 – heat-killed *mycobacterium vaccae*, TTF – time to treatment failure, TTP – time to progression, Vb – vinblastine, vs – versus, w – week(s).

^aBased on 213 patients with measurable disease

^bSurvival was converted from weeks to months using 1 wk = 0.229984378 months

^cOther included mixed and sarcomatous cell types

^dPR included partial response and regression

^eTwo different median survivals were reported. The median survival reported on the survival curve was used.

The remaining four studies included only small numbers of patients and lacked the power to reach any meaningful conclusions. Sorensen et al (17) randomized 31 patients to either doxorubicin or cyclophosphamide as single agents. No objective responses were observed in either treatment arm. White et al (13) randomized 25 patients with MPM along with 95 non-small cell lung cancer patients to either cisplatin and etoposide or infusional carboplatin. No objective responses were observed with the infusional carboplatin (8% vs 0%, respectively); however, survival for the two treatment arms was similar (4.3 months vs 5.0 months). O'Brien et al (12) found no benefit from the addition of SRL172 (*Mycobacterium vaccae*) to combination chemotherapy, and Cantwell et al (16) observed no activity of an experimental platinum analogue, JM9, in comparison to carboplatin (response rate, 0% vs 22%, respectively).

Noncomparative Studies

Non-platinum single-agent chemotherapy

A large number of phase II trials of single-agent chemotherapy were identified, totaling 1,673 patients enrolled in 52 trials of various agents (18-69). However, these studies provide weak evidence on which to base decisions about systemic therapy for MPM. In view of the heterogeneous nature of these phase II trials, the studies were separated into subgroups based on the type of chemotherapy evaluated in the trial (alkylating agents, anthracyclines, taxanes, vinca alkaloids, gemcitabine, antimetabolites, topoisomerase inhibitors, and experimental agents), and an aggregate response rate was determined for each group.

Alkylating agents

Seven trials involving 194 patients used temozolomide, ifosfamide, or cyclophosphamide in differing schedules and are shown in Appendix 1, Table A1 (18-24). The combined intention-to-treat (ITT) response rate for those trials was 4.6% (95% CI 1.8% to 7.5%). Grade 3 and 4 neutropenia ranged from 7% to 50%, and there were four treatment-related deaths. Other frequent toxicities included nausea, vomiting, and neurologic toxicity (encephalopathy). Van Meerbeeck et al attempted to assess QOL using a symptom checklist adapted from the European Organization for Research and Treatment of Cancer (EORTC) questionnaires (18); however, the questionnaire completion rate after baseline was low and interpretation of the results was therefore limited.

Anthracyclines

Ten phase II studies involving 319 patients evaluated conventional anthracyclines, liposomal anthracyclines, and mitoxantrone (25-34) (Appendix 2, Table A2). Response rates varied from 0% to 26%, with an overall ITT response rate of 6.1% (95% CI 3.6% to 8.7%). Major toxicities included neutropenia, nausea and vomiting, and skin toxicity (with liposomal preparations). No formal QOL measures were included, but Colbert et al (33) reported that 53% of patients with chest pain reported improvement in that symptom on treatment.

Taxanes

Four studies including 111 patients examined taxanes as a single-agent chemotherapy (35-38) (Appendix 1, Table A3). With the exception of one study by Vorobiof et al (35), the response rates were less than 10% (overall ITT response rate 5.1% [95% CI 1.2% to 9.1%]). Seven deaths due to treatment were observed. No study evaluated patient QOL.

Vinca alkaloids

Five studies involving 115 patients tested vinca alkaloids (39-43) (Appendix 1, Table A4). The overall ITT response rate was 3.6% (95% CI 0.4% to 6.8%). Steele et al (39) observed an ITT response rate of 24% with single-agent vinorelbine and a high rate of grade 3 and 4 neutropenia (62%). Other major toxicities included constipation (10%) and phlebitis

(14%). QOL was assessed using the Rotterdam Symptom Checklist. Improvements were seen in lung symptoms (48%), physical symptoms (41%), and psychological well being (76%). Little activity was seen in the four trials evaluating older vinca alkaloids (40-43).

Gemcitabine

Three trials examined gemcitabine as a single-agent chemotherapy (44-46) (Appendix 1, Table A5). Response rates varied from 0% to 31% with a combined ITT response rate of 6.7% (95% CI 1.2% to 12.2%), and median survival ranged from 4.7 months to 8 months.

Antimetabolites

Nine regimens reported in eight papers evaluated a variety of antimetabolites (34,47-53) (Appendix 1, Table A6). A total of 319 patients were included in those studies, with an overall ITT response rate of 9.0% (95% CI 6.0% to 11.9%). Only one study, by Scagliotti et al (49), assessed QOL, using the Lung Cancer Symptom Scale. The authors reported an improvement in the patient-reported global QOL as well as the observer-reported total score for those patients who responded to treatment.

Topoisomerase inhibitors

Topoisomerase inhibitors were evaluated in five regimens reported in four papers (54-57) (Appendix 1, Table A7). There was no observed activity with either topotecan or irinotecan and minimal activity with etoposide as a single agent (ITT response, 4.9% [95% CI 1.0% to 8.8%]).

Experimental agents

Little activity was observed with the experimental agents evaluated in 12 phase II trials (58-69) (Appendix 1, Table A8). Mikulski et al (61) conducted a large phase II trial (105 patients) using ranpirnase and obtained an ITT response rate of 3.8% with a median survival of 6 months. That agent has been taken into phase III trials for evaluation. Of the other experimental agents involved in phase II trials, dihydroazacytidine (62) showed the most promise with an ITT response rate of 16.3% and median survival of 6.7 months.

Non-platinum-based combination chemotherapy

Twelve trials have evaluated non-cisplatin-containing chemotherapy combinations (70-81) (Appendix 1, Table A9). Non-cisplatin-containing combinations appear to have a small increase in activity in comparison to single agents. The overall ITT response rate for those trials was 10.4% (95% CI 6.8% to 14.1%) compared to 6.4% (95% CI 5.3% to 7.5%) for single agents. Seven of the trials contained an anthracycline (70-76). Grade 3 to 4 neutropenia occurred in 7% to 87% of patients, with five studies reporting rates of 27% or higher (72,73,77,79).

Pinto et al treated 22 patients with mitoxantrone, methotrexate and mitomycin-C (79). They observed a 32% response rate and also assessed symptom improvement. Sixty-eight percent of patients reported improvement in dyspnea and 33% of patients who reported pain as an initial symptom described improvement in their pain.

Platinum-based single-agent and combination chemotherapy

A total of 35 trials have evaluated a platinum analogue in the treatment of patients with malignant mesothelioma (82-116). These trials vary in the treatment strategy (chemotherapy as either a single agent (82-90) or in combination (91-116)), route of administration (intrapleural vs intravenous), and type of platinum analogue (cisplatin vs carboplatin vs oxaliplatin vs experimental platinum analogues).

There were nine trials of single-agent chemotherapy (five cisplatin, three carboplatin, and one platinum analogue ZD0473) (82-90) (Appendix 1, Table A10). Platinum analogue ZD0473 was evaluated in a study by Giaccone et al (90) and demonstrated no activity in MPM. The response rate to single agent cisplatin was higher than carboplatin (ITT response: 20.0% vs 10.1%, respectively); however, these results were derived from only 197 patients in total and there was overlap of the 95% confidence intervals for these values. Toxicity was not well documented in the single-agent cisplatin trials. However, Planting et al (82) reported that 70% of patients had grade 3 to 4 thrombocytopenia, and 14% had grade 3 neutropenia. Rebattu et al (83) reported that 46% of patients had grade 3 to 4 nausea and/or vomiting, and 8% had grade 3 leukopenia.

More trials with greater numbers of patients (790 patients in total) have evaluated cisplatin in combination with other drugs (91-116) (Appendix 1, Table A11). The pooled data suggest that combining cisplatin with other drugs does not improve the response rate greatly. The overall ITT response rate for platinum combinations was 24.9% (95% CI 22.0% to 27.9%). The highest response rates were observed when a platinum agent was combined with an anthracycline (combined ITT response rate, 32.4% [95% CI 25.6% to 39.2%]) or either gemcitabine or irinotecan (combined ITT response rate, 26.1% [95% CI 21.5% to 30.7%]). Formal QOL was conducted in the study by Nowak et al (106). The authors reported that those patients who responded had greater improvement on the European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Cancer (EORTC-QLQ-C30) global QOL scale compared to those that did not respond ($p=0.006$); however, the effect did not persist past the completion of treatment. Pennucci et al (92), Breau et al (95), Ardizzoni et al (96), Middleton et al (101), Favaretto et al (104), Pinto et al (105), Byrne et al (108), and Kasseyet et al (109) all observed improvements in symptoms in responding patients as well as in some patients with stable disease. High levels of hematological toxicity were reported in most trials. Additional toxicities included grade 3 to 4 nausea/vomiting in 12% to 77% of patients, grade 3 diarrhea in 2% to 10% of patients, grade 3 to 4 infection in 4% to 9% of patients, and two renal toxicities (95,97) with one of these patients developing renal failure (97).

Combination chemotherapy and immunotherapy

There have been 12 studies combining chemotherapy with an immunomodulator such as interferon or interleukin (117-128) (Appendix 1, Table A12). Chemotherapy regimens in nine of the 12 studies have included cisplatin or carboplatin (120-128). The overall ITT response rate was 12.0% (95% CI, 8.7% to 15.3%). Response rates for combination chemotherapy and interferon were similar to those for single-agent chemotherapy and interferon. Additional toxicities from the addition of interferons or interleukin included asthenia and fever. None of the studies assessed QOL, and only one study (121) made reference to symptom improvement.

DISCUSSION

No studies comparing chemotherapy to BSC for patients with MPM were identified. Therefore, there is no evidence to answer the question of whether palliative chemotherapy improves survival in comparison to BSC for patients with MPM. Similarly, there is no level I or II evidence demonstrating that palliative chemotherapy improves QOL in comparison to BSC for patients with MPM. However, evidence from two large randomized trials comparing single-agent chemotherapy to combination chemotherapy showed significantly improved survival with combination chemotherapy. As single-agent cisplatin is unlikely to reduce survival in this patient population, these studies provide indirect evidence of a survival and QOL benefit from chemotherapy for patients with MPM. Further evidence comes from a recently published small trial that did not meet the inclusion criteria for this review, in which patients with MPM were randomized to immediate versus delayed chemotherapy. Patients randomized to immediate

chemotherapy had a small improvement in survival (14 vs 10 months, respectively) but this was not statistically significant (133).

A wide variety of agents have been tested either singly or in combination in patients with MPM. In uncontrolled studies, combination chemotherapy regimens appear to have slightly higher response rates than single-agent chemotherapy. The highest response rates have been seen with platinum-based chemotherapy regimens. Cisplatin as a single agent has a higher response rate than carboplatin. Based on those phase II data, cisplatin is the preferred platinum agent for use in the treatment of MPM. There is no evidence to support the addition of interferons or interleukin to chemotherapy in patients with MPM. Such combinations appear no more active than cisplatin-based chemotherapy but are associated with additional toxicity from the interferon or interleukin.

CONCLUSION

Prior to 2003, there was no standard chemotherapy regimen for the treatment of patients with malignant mesothelioma. The results of one large randomized trial presented at the 2002 meeting of ASCO, and subsequently published (11), make it reasonable to consider pemetrexed 500 mg/m² and cisplatin 75 mg/m² every 3 weeks, with vitamin supplementation with B₁₂ 1000 µg monthly and folic acid 0.4-1.0 mg in the treatment of patients with symptomatic MPM who are of good performance status (ECOG 0-1). Both vitamin supplements should be started before the administration of pemetrexed. Another recently published randomized study (10), comparing cisplatin and raltitrexed to cisplatin alone, has demonstrated superior survival for this combination regimen but non-significant improvements in response rate and progression-free survival. Therefore, the evidence supporting the use of cisplatin and pemetrexed is stronger. However, it is reasonable to consider the use of raltitrexed 3 mg/m² and cisplatin 80 mg/m² every three weeks, if pemetrexed is not available. The routine substitution of carboplatin for cisplatin is not recommended. Practitioners should select therapy based on the treatment options available, convenience, goals of therapy, and potential adverse effects. Given the limited amount of high-quality evidence on the role of chemotherapy in MPM and the poor treatment results for this disease, patients with mesothelioma should still be encouraged to participate in clinical trials of treatment for this disease.

ONGOING TRIALS

The National Cancer Institute's clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for reports of new or ongoing trials that involved chemotherapy for patients with MPM. Sixty-four trials were closed to recruitment as of April 2, 2004. The following trials were active as of April 2, 2004:

Protocol IDs	Title and details of trial
ALFACELL-P30-302, NCI-V97-1273	ONCONASE Plus Doxorubicin Versus Doxorubicin Alone For Patients With Malignant Pleural or Peritoneal Mesothelioma Who Have Had No More Than One Prior Chemotherapy Regimen. Outcomes: efficacy, toxicity, survival, quality of life. Projected accrual: 300 patients. Status: active. Summary last modified: 09/2005. Accessed October 18, 2005. Available at: http://www.cancer.gov/clinicaltrials/view_clinicaltrials.aspx?version=healthprofessional&cdrid=65639&protocolsearchid=852232 .
BC-MA-2	Phase II Study of Antineoplastons A10 and AS2-1 in Patients With Stage IV Mesothelioma. Outcomes: response, tolerance, adverse effects. Projected accrual: 20-40 patients. Status: active. Summary last modified: 09/2003. Accessed October 18, 2005. Available at: http://www.cancer.gov/clinicaltrials/view_clinicaltrials.aspx?version=healthprofessional&cdrid=66551&protocolsearchid=854600 .

- BTS-MRC-MS01, EU-20349, ISRCTN-54469112 Phase III Randomized Study of Active Symptom Control With Versus Without Chemotherapy in Patients With Malignant Pleural Mesothelioma. Outcomes: overall survival, adverse effects, symptom palliation, response, quality of life. Projected accrual: 840 patients within four years. Status: active. Summary last modified: 12/2003. Accessed October 18, 2005. Available at: http://www.cancer.gov/clinicaltrials/view_clinicaltrials.aspx?version=healthprofessional&cdrid=347461&protocolsearchid=854612.
- MSKCC-03078, LILLY-H3E-US-JMGA Phase II Study of Neoadjuvant Pemetrexed Disodium and Cisplatin Followed by Extrapleural Pneumonectomy and Radiotherapy in Patients With Stage I, II, or III Pleural Mesothelioma. Outcomes: response, survival, adverse effects. Projected accrual: 77 patients. Status: active. Summary last modified: 10/2003. Accessed October 18, 2005. Available at: http://www.cancer.gov/clinicaltrials/view_clinicaltrials.aspx?version=healthprofessional&cdrid=339681&protocolsearchid=854638.
- NCI-2710, UCCRC-11046A Phase II Randomized Study of Gemcitabine and Cisplatin With or Without Bevacizumab in Patients With Malignant Mesothelioma. Outcomes: response, time to progression, survival, toxicity. Projected accrual: 106 patients within 16 months. Status: active. Summary last modified: 10/2005. Accessed October 18, 2005. Available at: http://www.cancer.gov/clinicaltrials/view_clinicaltrials.aspx?version=healthprofessional&cdrid=69058&protocolsearchid=852275.
- NCT00061477, 7214 ALIMTA (pemetrexed) Plus Gemcitabine (Gemzar) for Patients with Malignant Pleural or Peritoneal Mesothelioma who have not had previous chemotherapy. Outcomes: safety, adverse effects, efficacy, response, palliation. Projected accrual: not available. Status: active. Summary last modified: not available. Accessed October 18, 2005. Available at: http://www.cancer.gov/clinicaltrials/view_clinicaltrials.aspx?version=healthprofessional&cdrid=352408&protocolsearchid=854664.
- UCCRC-11046A, NCI-2710 Phase II Randomized Study of Gemcitabine and Cisplatin With or Without Bevacizumab in Patients With Malignant Mesothelioma. Outcomes: response, toxicity, survival, adverse effects. Projected accrual: 106 patients within 16 months. Status: active. Summary last modified: 10/2005. Accessed October 18, 2005. Available at: http://www.cancer.gov/clinicaltrials/view_clinicaltrials.aspx?version=healthprofessional&cdrid=69058&protocolsearchid=854672.

CONFLICT OF INTEREST

The members of the Lung DSG disclosed potential conflicts of interest relating to the topic of this evidence summary. One of the lead authors and two DSG members reported membership on an advisory board of Eli Lilly, the pharmaceutical company that manufactures pemetrexed (Alimta®). Two DSG members reported additional involvement with Eli Lilly, including research involvement, research funding, provision of consultancy and expert testimony, ownership interests, or receipt of honoraria.

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Appendix 1. Phase II studies of chemotherapy with malignant pleural mesothelioma.

Table A1. Non-comparative studies of single-agent chemotherapy involving temozolomide, ifosfamide or cyclophosphamide.

Author, Year (Reference)	Inclusion criteria	Intervention	Number of patients	Histology	Response	Response rate (ITT)	PFS/ TTP/TTF	Overall Median survival	Toxicity	Quality of Life
van Meerbeeck 2002 (18)	MPM, bidimensionally measurable, PS 0-2, no prior CT	T 200mg/m ² po, d1-5 q4w	30 entered 27 eval	Epi 17 Non-Epi 8 Other 2	CR 0 PR 1 SD 11	4% (95% CI, 0.1-19) ITT 3%	PFS at 6mo, 20% (95% CI, 6-34%)	8.2mo (95% CI, 3.9-11.0mo) (1-yr, 30%, 95% CI, 10-50%)	G3/4 (NCIC-CTC) in 30 patients: gran 7%, leuk 3%, platelets 10%, febrile neut 3%, infection 3%, nausea 13%, vomiting 13%, dyspnea 10%, motor neuro 3%	High drop-out rate - general QOL tends to decrease before stopping treatment
Andersen, 1999 (19)	Unresectable MM, PS 0-3, no prior CT or RT, bidimensionally measurable disease	Ifos 3g/m ² + mesna d1-3 q3w	29 entered 23 eval for response 26 eval for toxicity	Epi 18 Sar 0 Mixed 8	CR 0 PR 1 SD 9	4% (95% CI, 0-11) ITT 3%	NR	10mo	10 G3/4 neuro, 19 G3/4 leuk, 10 G3/4 N/V, 2 G3/4 infection	NR
Icli, 1996 (20)	MM, measurable disease, symptomatic, PS 0-2, prior CT allowed	Grp A: Ifos 2.3g/m ² d1-5 q3w + mesna Grp B: Ifos 1.2g/m ² d1-5 q3w +mesna	15 entered 13 eval 16 entered & eval	Overall: Epi 28 Other 1	Grp A: CR 0 PR 5 SD 5 Grp B: CR 0 PR 1 SD 6	Grp A: 38% ITT 33% Grp B: 6% ITT 6%	NR NR	8mo 9mo	Grp A tox: 31% G3 N/V, 31% G3/4 leuk, 8% G3 hematuria, 15% G3 neuro (somnolence and hallucinations) Grp B tox: 12% G3 N/V, 19% G3/4 leuk, 6% G3 neuro (as above)	NR

Falkson, 1992 (21)	MM I, measurable or evaluable disease, PS 0-2, no prior CT	Ifos 1.5g/m ² d1-5 q3w +mesna	43 entered 39 eval	Epi 10 Other 16	CR 0 PR 1 SD 24	3% (90% CI, 0.1-12) ITT 2%	TTF 2.5mo	6.9mo	2 treatment related deaths, 45% G3/4 hematologic, 12% G3 V, 7% G3 neuro, 2% G5 acute pulmonary edema, 2% G5 acute renal failure	NR
Zidar, 1992 (22)	MM, PS 0-2, unresectable, bidimensionally measurable disease, ≤ no more than one prior CT treatment; prior sx or RT allowed	Ifos 2g/m ² d1-4 q3w, cont infusion +mesna	30 entered 26 eval	Epi 20 Sar 4 Mixed 2	CR 0 PR 2 SD 13	8% (95% CI 1-25) ITT 7%	NR	6.5mo	2 deaths on treatment, 1 (4%) G4 cerebral depression and myelotoxicity, 1 G3 neutropenia 50% G3/4 gran, 8% G3/4 anemia, 11% G3 thromb, 8% G3 N/V	NR
Alberts, 1988 (23)	MM, PS 0-2, measurable disease	Ifos 1.2g/m ² d1-5 (10 pts) q3w + mesna Ifos 1.5 g/m ² d1-5 +mesna(7pts)	17 entered & eval	Epi 7 Sar 1 Mixed 7 Other 2	CR 0 PR 4	23% (95% CI, 6-48)	NR	9mo	29% G3 N/V	NR
Anderson, 1988 (24)	MM, symptomatic, KPS ≤50%	Cy 2.5g/m ² over 24 hrs q3w	14 entered 13 eval	Epi 3 Sar 2 Mixed 2 Other 6	CR 0 PR 3 SD 5	23% ITT 21%	NR	6mo	7 infection	Symptoms improved in 6 (no details)
TOTAL			194 entered 174 eval for resp		0/18 (CR/PR)	5.3% (95% CI 2.1-8.5) ITT 4.6% (95% CI 1.8-7.5)				

Notes: CI – confidence interval, cont – continuous, CR – complete response, CT – chemotherapy, Cy – cyclophosphamide, d – day(s), eval – evaluable, Epi – epithelial, G – grade, gran – granulocytopenia, Grp – group, Ifos – ifosfamide, ITT – intention to treat, KPS – Karnofsky performance status, leuk – leukopenia, MM – malignant mesothelioma (pleural or peritoneal), mo – month(s), MPM – malignant pleural mesothelioma, NCIC-CTC – National Cancer Institute of Canada Common Toxicity Criteria, neuro – neurotoxicity, neut – neutropenia, NR – not reported, N/V – nausea and vomiting, PFS- progression-free survival, plt – platelet(s), po – orally, PR – partial response, PS – performance status, pts – patients, q – every, QOL – quality of life, resp – response, RT – radiotherapy, Sar – sarcomatous, SD – stable disease, sx – surgery, T – temozolomide, thromb – thrombocytopenia, tox – toxicity, TTF – time to treatment failure, TTP – time to progression, V – vomiting, w – week(s).

Table A2. Non-comparative studies of single-agent chemotherapy involving anthracyclines, liposomal anthracyclines or mitoxantrone.

Author, Year (Reference)	Inclusion criteria	Intervention	Number of patients	Histology	Response	Response rate (ITT)	PFS/ TTP	Overall Median survival	Toxicity	Quality of Life
Steele, 2001 (25)	MPM, PS 0-2, no prior CT or RT, measurable disease	Liposomal Daunorubicin 120mg/m ² q3w	14 entered 14 eval for resp 11 eval for tox	Epi 9 Sar 0 Mixed 5	CR 0 PR 0 SD 9	0%	NR	6.1mo	64% G3/4 neut, 29% G3/4 infection	NR
Baas, 2000 (26)	MM, no prior CT, PS 0-2, measurable disease	Liposomal Dx 45mg/m ² q4w	33 entered 31 eval for resp 32 eval for tox	Epi 17 Sar 6 Mixed 3 Other 5	CR 0 PR 2	6% (95% CI, 0.2-20.2)	5mo	13mo	10% G3/4 anemia, 16% G3/4 SOB, 6% G3/4 N, 6% skin tox, 3% G3 thromb, 6% G3/4 cardiac toxicity, 6% G3/4 infection	NR
Oh, 2000 (27)	MM, prior CT allowed	Liposomal Dx 50mg/m ² d1 q4w	24 entered 23 eval	Epi 14 Sar 3 Mixed 1 Other 6	CR 0 PR 0 SD 10	0%	NR	8.5mo	No DRD, 38% G3 skin tox, 13% G3/4 neut	NR
Mattson, 1992 (28)	MM, KPS >60, measurable or assessable disease, no prior CT	Epirubicin 110mg/m ² q3w	63 entered 48 eval for resp	Epi 17 Sar 5 Mixed 28 Other 2	CR 0 PR 7 SD 19	15% (95% CI, 6.1-27.8) ITT 11%	NR	9.2mo	No DRD, 27% G3/4 leuk, 4% G3/4 plt, 20% G3/4 N/V, no symptomatic cardiac dysfunction but 3 significant decrease in LVEF	NR
Magri, 1991 (29)	MM, measurable disease, no prior CT, KPS ≥40	Epirubicin 75mg/m ² q3w	23 entered 21 eval	NR	CR 0 PR 1 SD 11	5% ITT 4%	NR	7.5mo	No G3/4 toxicity	NR
Van Breukelen, 1991 (30)	MPM, KPS ≤60, no prior CT or RT, measurable/evaluable disease	Mitoxantrone 14mg/m ² q3w	46 entered 34 eval for resp 38 eval for tox	Epi 25 Sar 3 Mixed 13	CR 0 PR 1 SD 21	2.9% ITT 2.2%	NR	4.5mo	16% G3/4 leuk, 10.5% G3/4 N/V	NR
Kaukel, 1990 (31)	MPM, histologically proven, KPS ≥60, measurable disease	Pirarubicin 70mg/m ² q3w	35 entered & eval	Epi 21 Sar 2 Mixed 9 Unknown 3	CR 0 PR 3 SD 19	8.6%	NR	10.5mo	20% G3/4 leuk, 6% G3 alopecia, 3% G3 N/V	NR

Eisenhauer, 1986 (32)	MM, no prior CT, PS 0-2, measurable disease	Mitoxantrone 12mg/m ² q3w	30 entered 28 eval	NR	CR 1 PR 1 SD 15	7.1% ITT 6.7%	NR	NR	36% G3/4 neut, 7.1% infection/fever	NR
Colbert, 1985 (33)	MM, no prior CT, PS 0-4, measurable or evaluable disease	Detorubicin 40mg/m ² d1-3 q3w x5 then 40mg/m ² d1 q3w	40 entered 35 eval (32 pleural, 3 peritoneal)	Epi 31 Sar 2 Mixed 2	CR 2 PR 7 SD 7	26% ITT 22.5%	NR	17mo	26% G3/4 N/V, 11% mucositis, 2 deaths from pulmonary edema, 3% FN	53% (8/15) of pts with complete relief of chest pain
Harvey, 1984 (34)	MM, KPS >60, prior CT with 5-FU	Dx 60mg/m ² q4w	11 entered (after PD on 5-FU)	Epi 3 Mixed 6 Other 2	CR 0 PR 1	9%	NR	4.5mo	Not well documented	NR
TOTAL			319 entered 280 eval for resp		3/23 (CR/PR)	6.9% (95% CI 4.1-9.8) ITT 6.1% (95% CI 3.6-8.7)				

Notes: 5-FU – 5-Fluorouracil, CI – confidence interval, CR – complete response, CT – chemotherapy, d – day(s), DRD – drug related deaths, Dx – doxorubicin, Epi – epithelial, eval – evaluable, FN – febrile neutropenia, G – Grade, ITT – intention to treat, KPS – Karnofsky performance status, leuk – leukopenia, LVEF – left ventricular ejection fraction, MM – malignant mesothelioma (pleural or peritoneal), mo – month(s), MPM – malignant pleural mesothelioma, neut – neutropenia, NR – not reported, N/V – nausea/vomiting, PD – progressive disease, PFS – progression-free survival, PR – partial response, PS – performance status, pts – patients, q – every, resp – response, RT – radiotherapy, Sar – sarcomatous, SD – stable disease, SOB – shortness of breath, thromb – thrombocytopenia, tox – toxicity, TTP – time to progression, w – week(s).

Table A3. Non-comparative studies of single-agent chemotherapy involving taxanes.

Author, Year (Reference)	Inclusion Criteria	Intervention	Number of patients	Histology	Response	Response rate (ITT)	PFS/TTP	Overall Median survival	Toxicity	Quality of Life
Vorobiof, 2002 (35)	MPM, PS 0-2, no prior CT, RT, or immunotherapy	Docetaxel 100mg/m ² q3w	31 entered 29 eval	NR	CR 0 PR 3 SD 17 ^a	10.3% ITT 9.7%	TTP 3.5mo	12.2mo	3 early deaths, G3/4 toxicities: 3.4% each anemia, nail disorders, infection, weight loss, and hallucinations 10.3% each neut and mucositis, 6.9% each diarrhea and alopecia	NR
Belani, 1999 (36) abstract	MM, PS 0-2, no prior CT	Docetaxel 100mg/m ² q3w	20 entered 19 eval	NR	CR 0 PR 1 SD 3	5% (95% CI, 0.16-26.4)	NR	NR	3 early deaths, 42% G4 gran, 90% G4 leuk, 11% G4 V/D	NR
Vogelzang, 1999 (37)	MM, no prior CT, PS 0-2	Paclitaxel 250mg/m ² q3w, 24hr infusion + G-CSF	35 entered 30 eval for resp	Epi 23 Sar 6 Mixed 2	CR 0 PR 3 SD 19	9% (95% CI, 2-23)	FFS 3mo (95% CI, 1.7-14.1mo)	5mo (95% CI, 1.9-9.6mo)	1 death from pneumonia, 40% G4 gran, 17% infection (1 death), 11% neuro, 18% fatigue & malaise	NR
van Meerbeeck, 1996 (38)	MM, no prior CT, measurable disease PS 0-2	Paclitaxel 200mg/m ² q3w	25 entered 23 eval	Epi 14 Sar 2 Mixed 7 Other 1	CR 0 PR 0 SD 10	0%	NR	9mo	1 death due to malignant disease, 22% G3/4 neut, 9% G3/4 N/V, 9% G3 myalgia, 13% G3 neuro, 4% G3 mucositis	NR
TOTAL			111 entered 101 eval		0/7 (CR/PR)	5.6% (95% CI 1.3-9.9) ITT 5.1% (95% CI 1.2-9.1)				

Notes: CI – confidence interval, CR – complete response, CT – chemotherapy, Epi – epithelial, eval – evaluable, FFS – failure free survival, G – grade, gran – granulocytopenia, G-CSF – filgrastim, ITT – intention to treat, leuk – leukopenia, MM – malignant mesothelioma (pleural or peritoneal), mo – month(s), MPM – malignant pleural mesothelioma, neuro – neurotoxicity, neut – neutropenia, NR – not reported, N/V – nausea/vomiting, PFS – progression-free survival, PR – partial response, PS – performance status, q – every, resp – response, RT – radiotherapy, Sar – sarcomatous, SD – stable disease, TTP – time to progression, V/D – vomiting/diarrhea, w – week(s).

^a – SD included the number of patients with SD plus those with a minor response.

Table A4. Non-comparative studies of single-agent chemotherapy involving vinca alkaloids.

Author, Year (Reference)	Inclusion Criteria	Intervention	Number of patients	Histology	Response	Response rate (ITT)	PFS/TTP	Overall Median survival	Toxicity	Quality of Life
Steele, 2000 (39)	MM, unresectable, measurable disease, PS 0-2, no prior CT	VNR 30mg/m ² weekly for 6w	29 entered & eval	Epi 17 Sar 2 Mixed 10	CR 0 PR 7 SD 16	24% (95% CI, 10-44)	NR	10.6mo	62% G3/4 neut, 10% G3/4 constipation, 14% G3/4 phlebitis, 4% G3/4 neutropenic sepsis, 41% leuk	Rotterdam. Improved lung symptoms 48%, physical 41%, psych 76%, activity level improvement 17% and worsening 52%
Martensson, 1989 (40)	MM, measurable disease, no prior CT	VCR 1.3mg/m ² q1w x 4 then q2w	23 entered & eval	Epi 19 Sar 3 Mixed 1	CR 0 PR 0	0%	NR	7mo	No severe toxicities reported	NR
Cowan, 1988 (41)	MM, unresectable, PS 0-2, evaluable lesion, <2 prior CT	Vb 1.4mg/m ² d1-5 q3w	22 entered 20 eval for resp 22 eval for tox	NR	CR 0 PR 0 SD 9	0%	NR	3.0mo	No severe toxicities reported	NR
Boutin, 1987 (42)	MM, no prior CT, KPS ≤60%	Vindesine 2mg/m ² d1,2 q2w	21 entered & eval	Epi 14 Sar 2 Mixed 5	CR 0 PR 0 SD 8	0%	NR	NR	Not well documented, 1 neuro toxicity	NR
Kelsen, 1983 (43)	MM, prior CT allowed, measurable or evaluable disease, KPS 40-90%	Vindesine 3mg/m ² weekly x 4-6w then q2w	20 entered 17 eval	NR	CR 0 PR 1 SD 1	6% (95% CI, 0-17) ITT 5%	NR	NR	Not well documented, 2 severe peripheral neuropathy, 25% constipation	NR
TOTAL			115 entered 110 eval for resp		0/8 (CR/PR)	3.7% (95% CI 0.4-7.0) ITT 3.6% (95% CI 0.4-6.8)				

Notes: CI – confidence interval, CR – complete response, CT – chemotherapy, d – day(s), Epi – epithelial, eval – evaluable, G – Grade, ITT – intention to treat, KPS – Karnofsky performance status, leuk – leukopenia, MM – malignant mesothelioma (pleural or peritoneal), mo – month(s), neuro – neurotoxicity, neut – neutropenia, NR – not reported, PFS – progression-free survival, PR – partial response, PS – performance status, psych – psychological, q – every, resp – response, Sar – sarcomatous, SD – stable disease, tox – toxicity, TTP – time to progression, Vb – vinblastine, VCR – vincristine, VNR – vinorelbine, w – week(s).

Table A5. Non-comparative studies of single-agent chemotherapy involving gemcitabine.

Author, Year (Reference)	Inclusion Criteria	Intervention	Number of patients	Histology	Response	Response rate (ITT)	PFS/TTP	Overall Median survival	Toxicity	Quality of Life
Kindler, 2001 (44)	MM, unresectable, measurable or evaluable disease, PS 0-2, no prior CT	Gem 1500mg/m ² d1,8,15 then q4w	17 entered & eval	Epi 9 Sar 5 Mixed 3	CR 0 PR 0 SD 8	0%	TTF 1.7mo (95% CI, 1.5-2.4mo)	4.7mo	12% G3/4 neut, 12% G3/4 anemia, 12% G3/4 infection, 1 death, 12% dyspnea, 12% malaise	NR
van Meerbeeck 1999 (45)	MM, no prior CT, bidimensionally measurable disease, PS 0-2	Gem 1250mg/m ² d1,8,15 then q4w	32 entered 25 eval for resp 27 eval for tox	Epi 18 Sar 3 Mixed 6	CR 0 PR 2 SD 15	7% (95% CI, 1-24) ITT 6%	NR	8 mo	30% G3/4 gran, 4% G4 thromb, 4% G3 infection, 11% FN, 22% G3/4 dyspnea, 4% hemolytic uremic syndrome, 11% G3 heart failure, 11% G3 N/V, 11% G3 hypertension, 7% G3/4 renal failure	NR
Bischoff, 1998 (46) Abstract	MM, no prior CT or RT, PS 0-2	Gem 1250mg/m ² d1,8,15 q4w	23 entered 16 eval	Epi 22 Mixed 1	CR 1 PR 4 SD 7	31% ITT 22%	NR	NR	NR	NR
TOTAL			72 entered 58 eval for resp		1/6 (CR/PR)	6.9% (95% CI 0.9-13.0) ITT 6.7% (95% CI 1.2-12.2)				

Notes: CI – confidence interval, CR – complete response, CT – chemotherapy, d – day(s), Epi – epithelial, eval – evaluable, FN – febrile neutropenia, G – grade, Gem – gemcitabine, gran – granulocytopenia, ITT – intention to treat, MM – malignant mesothelioma (pleural or peritoneal), mo – month(s), neut – neutropenia, NR – not reported, N/V – nausea/vomiting, PFS – progression-free survival, PR – partial response, PS – performance status, q – every, resp – response, RT – radiotherapy, Sar – sarcomatous, SD – stable disease, thromb – thrombocytopenia, tox – toxicity, TTF – time to treatment failure, TTP – time to progression, w – week(s).

Table A6. Non-comparative studies of single-agent chemotherapy involving antimetabolites.

Author, Year (Reference)	Inclusion Criteria	Intervention	Number of patients	Histology	Response	Response rate (ITT)	PFS/TT P	Overall Median survival	Toxicity	Quality of Life
Baas, 2003 (47)	MPM, no prior CT, PS 0-2	Raltitrexed 3.0mg/m ² d1 q3w x 2 (minimum)	24 entered & eval	Epi 21 Sar 1 Mixed 1 Unknown 1	CR 0 PR 5 SD 8	20.8% (95% CI, 7.1-42.2%)	Mean TTP 9.4mo	7mo (95% CI, 5.5-18.7mo)	4% each G4 anorexia and dyspnea; 13% G3 neut; 8% each G3 pleuritic pain, other pain, fatigue; 4% each G3 leuk, febrile neut, weight loss, diarrhea, nausea, vomiting, other neurological tox, chest pain, cough, dyspnea, and hepatic function	NR
Otterson, 2003 (48) abstract	MM, previously untreated, PS 0-2	Capecitabine 2500mg/m ² d1-14, 1w treatment free, up to 6 cycles	27 entered 26 eval	Epi 15 Mixed 8 Unknown 3	CR 0 PR 1 SD 10	3.8% ITT 3.7%	FFS 2.4mo	4.9mo	G3/4 toxicities: 12% each lymphopenia and fatigue, 15% diarrhea, 8% hand-foot syndrome. 1 toxic death.	NR
Scagliotti, 2003 (49)	Advanced MPM, no prior CT, KPS≥70, measurable disease	Pem 500mg/m ² d1 q3w (with or without FS with FA and vitamin B ₁₂)	64 entered & eval (43 FS, 21 NS)	Epi 45 Sar 8 Mixed 9 Other 2	<u>FS</u> CR 0 PR 7 SD 27 <u>NS</u> CR 0 PR 2 SD 6 Total CR/PR calculated from ITT%	ITT: 16.3% (95%CI, 6.8-30.7) ITT: 9.5% (95%CI, 1.2-30.4)	TTP: 4.8mo (95% CI, 4.4-6.1mo) TTP: 3.0mo (95% CI, 1.7-5.8mo)	13mo (95%CI, 8.2-∞mo) 8mo (95%CI, 4.8-14.5mo)	G3/4, FS vs NS: neut, 9% vs 52%, leuk, 9% vs 38% thromb, 2% vs 5%. No significant non-hematological tox	LCSS: improved patient-reported global QOL and observer-reported total score for responders.
Kindler, 1999 (50)	MM, not suitable for sx or RT, PS 0-2, measurable or evaluable disease, no prior CT, prior RT allowed	Edatrexate 80mg/m ² q1w x 8w	20 entered & eval	Epi 13 Sar 2 Mixed 5	CR 1 PR 2 Regression in 2 eval patients	ITT 15%	TTF 5.2mo	9.6 mo	G3/4 toxicities: 25% leuk, 25% gran, 15% plt, 45% infection, 45% pulmonary, 40% mucositis, 15% cardiac, 20% neuro, 2 deaths due to neutropenic sepsis	NR

Kindler (2), 1999 (50)	As above	Edatrexate 80mg/m ² q1w x 8 + leucovorin 15mg po q6h x4	40 entered 38 eval	Epi 23 Sar 7 Mixed 8	CR 0 PR 1 Regression in 5 eval patients	2.6% ITT 2.5%	TTF 3.4mo	6.6mo	G3/4 toxicities: 3% leuk, 3% gran, 4% infection, 5% mucositis, 16% pulmonary, 8% cardiac	NR
Vogelzang, 1994 (51)	MM, measurable or evaluabile disease, unresectable, no prior CT or RT, PS 0-2	Trimetrexate Cohort I (n=17): 6mg/m ² d1-5 q3w Cohort II (n=34): 10mg/m ² d1-5 q3w	52 entered 48 eval for resp	Epi 38 Sar 6 Mixed 6 Other 1	CR 0 PR 6 (2 from cohort I, 4 from cohort 2) SD 27	ITT 11.5%	Cohort I 1.5mo Cohort II 4.4mo	Cohort I 5.0mo Cohort II 8.9mo	G3/4 toxicities: Cohort I: 12% gran, 6% infection, 6% plt Cohort II: 6% infection (one toxic death from sepsis), 24% gran, 15% plts (12% G4), 12% N/V	NR
Solheim, 1992 (52)	MM, KPS >50%, symptomatic	Methotrexate 3g/m ² q10d x 4 then q3w x 4	63 entered 60 eval for resp	Epi 42 Sar 4 Mixed 16	CR 1 PR 21 SD 19	37% ITT 34.9%	NR	11mo	No toxicity in 42% of pts, 1 toxic death, 1 allergic reaction	NR
Harvey, 1984 (34)	MM, KPS >60	Fluorouracil 10-15mg/kg d1-5 q4w	20 entered & eval (18 pleural, 2 peritoneal)	Epi 7 Mixed 10 Fibrous 1 Other 2	CR 0 PR 1	5%	NR	5mo	Not well documented	NR
Dimitrov, 1982 (53)	MM	Methotrexate 1.5g/m ² +VCR 2mg q4w	9 entered & eval	Epi 5 Sar 1 Other 3	CR 3 PR 3	66.7%	NR	10mo	Not well documented; no DRD, leuk and oral mucositis	NR
TOTAL			319 entered 309 eval		5/49 (CR/PR)	9.4% (95% CI 6.4-12.4) ITT 9.0% (95% CI 6.0-11.9)				

Notes: CI – confidence interval, CR – complete response, CT – chemotherapy, d – day(s), DRD – drug related death(s), Epi – epithelial, eval – evaluable, FA – folic acid, FFS – failure free survival, FS – full supplementation, G – grade, gran – granulocytopenia, h – hour(s), ITT – intention to treat, KPS – Karnofsky performance status, LCSS – Lung Cancer Symptom Scale, leuk – leukopenia, MM – malignant mesothelioma (pleural or peritoneal), mo – month(s), MPM – malignant pleural mesothelioma, neuro – neurotoxicity, neut – neutropenia, NR – not reported, NS – not supplemented, N/V – nausea/vomiting, Pem – pemetrexed, PFS – progression-free survival, plt – platelet toxicity, po – orally, PR – partial response, PS – performance status, pts – patients, q – every, QOL – quality of life, resp – response, RT – radiotherapy, Sar – sarcomatous, SD – stable disease, sx – surgery, thromb – thrombocytopenia, tox – toxicity, TTF – time to treatment failure, TTP – time to progression, VCR – vincristine, vs – versus, w – week(s).

Table A7. Non-comparative studies of single-agent chemotherapy involving topoisomerase inhibitors.

Author, Year (Reference)	Inclusion Criteria	Intervention	Number of patients	Histology	Response	Response rate (ITT)	PFS/TTP	Overall Median survival	Toxicity	Quality of Life
Kindler, 2000 (54) Abstract	MM, PS 0-2, bidimensionally measurable and eval disease	CPT-11 125mg/m ² q1w x 4 q6w	28 entered & eval	Epi 18 Sar 5 Mixed 5	CR 0 PR 0 SD 8	0%	2.7mo	7.9mo	30% G3/4 neut, 22% G3/4 leuk, 45% G3/4 lymphopenia, 18% G3/4 diarrhea, 15% G3/4 N, 2 deaths due to infection	NR
Maksymiuk, 1998 (55)	MM, unresectable, no prior CT, recent surgery (<2w), measurable or eval disease	Topotecan 1.5mg/m ² d1-5 q3w	22 entered & eval	Epi 15 Other 7	CR 0 PR 0 SD 18	0%	2.3mo	7.6mo	86% G3/4 neut, 14% G3/4 thromb, 9% G3 malaise, 5% G3 infection, no toxic deaths	NR
TOTAL			50 entered 50 eval		0/0	0%				
Sahmoud, 1997 (56)	MM, no prior CT or RT, measurable disease, PS 0-2	Etop 150mg/m ² IV d1,3,5 q3w	49 entered 47 eval	Epi 8 Sar 21 Mixed 3 Other 5	CR 0 PR 2 SD 15	ITT 4% (95% CI, 1-15)	NR	6.7mo	6% G3/4 leuk, 4% G3/4 N/V, 2% G3/4 mucositis	NR
Sahmoud (2), 1997 (56)	As above	Etop 100mg po d1-21, 2w treatment free, then repeat	45 entered 41 eval	Epi 18 Sar 6 Mixed 5 Other 12	CR 0 PR 3 SD 14	7% (95% CI, 2-20) ITT 6.7%	NR	8.5mo	12% G3/4 leuk, 2% G3/4 thromb, 10% G3/4 N/V	NR
Tammilehto, 1994 (57)	MM, predominantly stage I&II, no prior CT or RT	Etop 100mg po d1-21 then repeat in 2w	23 entered 19 eval	Epi 11 Mixed 8	CR 0 PR 1 SD 15	5% ITT 4%	NR	17mo after diagnosis	No toxic deaths, no other details about toxicity reported	NR
TOTAL			117entered 107 eval		0/6 (CR/PR)	5.3% (95% CI 1.1-9.5) ITT 4.9% (95% CI 1.0-8.8)				

CI – confidence interval, CPT-11 – Irinotecan, CR – complete response, CT – chemotherapy, d – day(s), Epi – epithelial, Etop – etoposide, eval – evaluable, G – grade, ITT – intention to treat, IV – intravenous, leuk – leukopenia, MM – malignant mesothelioma (pleural or peritoneal), mo – month(s), N – nausea, neut – neutropenia, NR – not reported, N/V – nausea/vomiting, PFS – progression-free survival, po – orally, PR – partial response, PS – performance status, q – every, RT – radiotherapy, Sar – sarcomatous, SD – stable disease, thromb – thrombocytopenia, TTP – time to progression, w – week(s).

Table A8. Non-comparative studies of single-agent chemotherapy involving experimental agents.

Author, Year (Reference)	Inclusion Criteria	Intervention	Number of patients	Histology	Response	Response rate (ITT)	PFS/TTP	Overall Median survival	Toxicity	Quality of Life
Villano, 2004 (58) abstract	MPM, unresectable, measurable disease, PS 0-1	Imatinib mesylate, orally, 600mg/d for 28d (5pts reduced dose to 400mg/d)	17 entered eval: NR	Epi 80% Mixed 20%	CR 0 PR 0 SD NR	0%	PFS 1.7mo (95% CI, 1.6-3.2mo)	NR	In 41 cycles of imatinib: G3/4 toxicities: 12% N 12% dyspnea 6% each leuk, neut, fatigue, edema, rash	NR
Govindan, 2003 (59) abstract	MM, previously untreated	Gefitinib 500mg/d orally	43 entered 43 eval for resp 42 eval for tox	Epi 34 Sar 3 Mixed 5 Unknown 1	CR 0 PR 1 SD 20	2%	Median PFS 1.7mo (95% CI, 1.5-4.0mo)	5mo	2% G4 dehydration G3 toxicities: 10% diarrhea, 10% N, 7% each V, dehydration, fatigue, 5% skin rash	NR
Millward, 2003 (60) abstract	MPM, unresectable, PS 0-2, measurable disease, adequate organ function, only 1 prior CT regimen	Imatinib mesylate, orally, starting dose 800mg/d, 17 pts required dose reduction: 600mg/d (8), 400mg/d (5), <400mg/d (4)	29 entered 25 eval for resp 27 eval for tox	NR	CR 0 PR 0 SD 11	0%	NR	NR	G3 toxicities: 15% fatigue, 4% each V, anorexia, and edema. No G4 toxicities.	NR
Mikulski, 2002 (61)	MM, unresectable, PS 0-2, prior CT or RT allowed	Ranpirnase 480µg/m ² weekly	105 entered 81 eval for resp 105 eval for tox	Epi 50 Non-Epi 16 Other 39	CR 0 PR 4 SD 37	4.9% ITT 3.8%	median TTP 3.4mo	6.0mo (95% CI, 4.7-10.0mo)	NCIC-CTC G3/4: 6% asthenia, 2% N, 2% myalgia, 2% anorexia, 3% pain, 3% arthralgia, 4% peripheral edema, 2% hypotension, no DRD, 10 deaths on study and 11 within 30d of stopping medication	NR

Vogelzang, 1997 (62)	MM, PS 0-2, unresectable, measurable or eval disease, no prior CT	DHAC 1500mg/m ² /d d1-5 q3w	43 entered 41 eval for resp (2 primary peritoneal)	Epi 73%	CR 1 PR 6 SD 13	17% (95% CI, 7-32) ITT 16.3%	TTF 2.2mo	6.7mo	No hematologic G3/4 tox, 25% G3 chest pain, 20% G3 N/V, 15% G3 anemia, 23% G3/4 cardiac tox, 1 sudden death, 2 cardiac tamponade	NR
Hudis, 1992 (63)	MM, KPS 50-100, no prior CT, prior RT allowed, inoperable, measurable or eval disease	Menogaril 200mg/m ² q4w	22 entered & eval	NR	CR 0 PR 1 SD 6	ITT 4.5% (95% CI, 0.1-23)	NR	NR	No DRD, toxicity ≤G3, 32% pain at infusion site, 23% anorexia, 23% N/V, 19% mucositis	NR
Dhingra, 1991 (64)	MM, PS 0-2, inoperable, measurable disease, no prior CT or RT	DHAC 5g/m ² q4w	15 entered 14 eval for resp 15 eval for tox	NR	CR 0 PR 0 SD 3	0%	NR	4.7mo	No DRD, no hematologic tox, 13% G3 N/V, 7% G3 abdominal/chest pain	NR
Bajorin, 1987 (65)	MM, KPS >50, unresectable or recurrent, 9 pts prior CT, measurable or eval disease	Mit-C 10mg/m ² q4w x 3 then q6w	20 entered 19 eval	Epi 11 Sar 3 Mixed 2 Other 3	CR 0 PR 4	21% ITT 20%	NR	NR	Not documented 2 pts drug induced pulmonary tox	NR
Falkson, 1987 (66)	MM, PS 0-2, unresectable, eval disease, no prior CT	Acivicin 20mg/m ² /day d1-3 q3w	23 entered 21 eval (20 pleural, 2 peritoneal, 1 both)	Epi 5 Sar 2 Mixed 5 Other 11	CR 0 PR 0 SD 12	0%	NR	28w	13% neuro, 13% N/V	NR
Cantwell, 1986 (67)	MM, measurable or evaluable, no prior CT	Cb3717 ^a : 400 mg/ m ² (15pts) 300 mg/ m ² (3pts) q3w	18 entered & eval	NR	CR 0 PR 1	5.6% (95% CI, 0.1-27.3)	NR	NR	22% G3 N/V, 22% G3 liver tox	NR
Eagan, 1986 (68)	MM, PS 0-3, unresectable, measurable or evaluable, prior CT allowed	Diaziquone (AZQ) 30mg/m ² q4w	21 entered 20 eval (18 pleural, 2 peritoneal)	NR	CR 0 PR 0 SD 12	0%	TTP 1.8mo	5.9mo	45% N (35% mild), 25% V (20% mild), 5% stomatitis	NR

Falkson, 1983 (69)	MM, unresectable, evaluable disease, PS 0-3	m-AMSA 120mg/m ² q3w	20 entered 19 eval (17 pleural, 3 peritoneal)	NR	CR 0 PR 1 SD 12	5.3%	NR	6.2mo	10.5% G3 N/V, 10.5% G3 leuk,	NR
TOTAL			376 entered 323 eval ^b		1/18 ^b (CR/PR)	4.5% ^b (95% CI 2.3-6.7) ITT 4.0% (95% CI 2.0-5.9)				

Notes: Cb – carboplatin, CI – confidence interval, CR – complete response, CT – chemotherapy, d – day(s), DHAC – dihydroazacytidine, DRD – drug related deaths, Epi – epithelial, eval – evaluable, G – grade, KPS – Karnofsky performance status, ITT – intention to treat, leuk – leukopenia, m-AMSA – acridine derivative, Mit-C – mitomycin C, MM – malignant mesothelioma (pleural or peritoneal), mo – month(s), MPM – malignant pleural mesothelioma, N – Nausea, NCIC-CTC – National Cancer Institute of Canada Common Toxicity Criteria, neuro – neurotoxicity, neut – neutropenia, NR – not reported, N/V – nausea/vomiting, PFS – progression-free survival, PR – partial response, PS – performance status, pts – patient, q – every, resp – response, RT – radiotherapy, Sar – sarcomatous, SD – stable disease, thromb – thrombocytopenia, tox – toxicity, TTF – time to treatment failure, TTP – time to progression, V – vomiting, w – week(s).

^a – N¹⁰ – Propargyl-5, 8Dideazafolic Acid.

^b – The trial reported by Villano et al () was excluded from the pooled response rate calculation for the evaluable pts as the total number of evaluable pts was not reported.

Table A9. Non-comparative studies of non-platinum-based combination chemotherapy.

Author, Year (Reference)	Inclusion criteria	Intervention	Number of patients	Histology	Response	Response rate (ITT)	PFS/TTP	Overall Median survival	Toxicity	Quality of Life
Anthracycline regimens										
Okuno, 2003 (70) abstract	MPM, measurable disease, PS 0-2, ≤1 prior CT regimen	Gem 1000 mg/m ² d1,8 + Ep 90 mg/m ² d1 q3w x 6 Due to toxicity concerns, doses were modified to: Gem 750 mg/m ² , Ep 70 mg/m ²	23 entered & eval	Epi 15 Sar 5 Mixed 3	CR 0 PR 4	ITT 17.4%	TTP 3.4mo	NR	22%/78% G3/G4 hematological toxicity 61%/4% G3/G4 non-hematological toxicity No toxic deaths	NR
Baas, 2002 (71) abstract	MPM, measurable or evaluable disease, PS 0-2, no prior CT	Grp1:HD-MTX 3g total dose q2w x 3 Grp2:HD-MTX 3g +Dx 40mg total dose q2w x 3	G1: 10 entered 8 eval G2: 19 entered 16 eval	NR	HD-MTX CR 0/PR 0/SD 4 HD-MTX+Dx CR 0/PR 2/SD 7	0% 12.5% ITT 10.5%	NR	7mo 7mo	Of 138 courses overall: anemia 3%, FN 10%, renal 10%, mucositis 6%	NR
Dirix, 1994 (72)	MM, measurable disease, PS 0-1, no prior CT or RT	Dx 75 mg/m ² + Ifos 5g/m ² + GM-CSF 250 µg/m ² (12 pts) or G-CSF 5 µg/kg (12pts) q3w	24 entered 22 eval for resp 24 eval for tox	Epi 15 Sar 2 Mixed 6 Other 1	CR 0 PR 7	32% (95% CI, 13-51) ITT 29%	NR	7mo	87% G3/4 neut, 89% G3/4 leuk, 42% G3/4 thromb, 25% G3/4 N/V, 75% FN, 1 cerebral hemorrhage (fatal due to G3 thromb)	NR
Magri, 1992 (73)	MM, measurable disease, KPS ≥40 (range 60-100), no prior CT	Ep 75mg/m ² d1+ Ifos 1.8g/m ² d1-5 q3w	17 entered & eval	NR	CR 0 PR 1 SD 8	ITT 6%	NR	6mo	No DRD, 29% G3/4 myelosuppression, 1 pt transient neuro (coma)	NR
Carmichael, 1989 (74)	MM, measurable or assessable, PS 0-3	Ifos 5g/m ² d1 + Dx 40mg/m ² d1 q3w	17 entered 16 eval (16 pleural, 2 peritoneal)	NR	CR 0 PR 2	12.5% (95% CI, 1.5-38.3) ITT 11.8%	NR	7.9mo	94% G3/4 N/V, 7% G3 neut, 7% encephalopathy, 1 DRD	NR
Jett, 1982 (75)	MM, unresectable, no prior therapy, PS 0-2	(CAMEO) Cy 350mg/m ² d1 + Adr 25mg/m ² d1 + MTX 25mg/m ² d2 + Etop 80mg/m ² d1-3 + VCR 1.2mg/m ² d2, q4w 8 pts received RT to hemithorax during CT	12 entered 12 eval	NR	CR 0 PR 2 SD 8	17%	NR	6.5mo	Not well documented; 8% severe N/V, treatment d/c in 1 pt due to weight loss, VCR d/c in 1 pt due to neuro	NR

Chahinian, 1978 (76)	MM, progressive disease, previous CT or RT allowed	Dx 25mg/m ² d1-3 + 5-azacytidine 120mg/m ² d1-5 q4w	8 entered & eval	NR	CR 2 PR 0 SD 2	25%	NR	NR	Not well documented; 40% (3pts) leuk, 13% (1pt) thromb	NR
SUBTOTAL			130 entered 122 eval (excluding single arm MTX)		2/18 (CR/PR)	12.8% (95% CI 7.0-18.5) ITT 11.7% (95% CI 6.3-17.1)				
Other regimens										
Janne, 2004 (77) abstract	MPM, unresectable, no prior CT, PS 0-2	Gem 1250mg/m ² d1, 8 + Pem 500mg/m ² d8 q3w x6 (maximum) (All pts received vitamin B ₁₂ , folic acid and steroid prophylaxis)	53 entered 34 eval for resp 41 eval for tox	Epi 28 Sar 3 Mixed 5 Other 5 (of 41pts)	CR 0 PR 7 SD 18	20.6% (95% CI, 9-38%) ITT 13.2%	NR	NR	Of 121 cycles: G3/4 toxicities: 33.1% neut, 5% fatigue, 3.3% neuro, 2.5% nausea, 1.7% asthenia, 1.7% anemia, 1.7% thromb	NR
Ferrari, 2002 (78) abstract	MM, PS 0-3	Gem 1000mg/m ² d1, 8 + CPT-11 200mg/m ² d1 q3w	15 entered 14 eval for resp 15 eval for tox	NR	CR 0 PR 2 SD 6	14.3% ITT 13.3%	NR	NR	NCIC-CTC: 1 pt (7%) each for G3 neut, G3 diarrhea, G4 vomiting and G4 dermat; no DRD	NR
Pinto, 2001 (79)	MM, measurable or assessable disease, KPS >70, no prior CT or RT	Mitoxantrone 10mg/m ² + MTX 35mg/m ² + Mit-C 7mg/m ² d1 q3w (Mit-C in alternate cycles)	22 entered & eval	Epi 14 Sar 1 Mixed 2	CR 1 PR 6 SD 7	32%	TTP 6mo	13.5mo	82% G3/4 neut, 14% G3/4 anemia, 23% G3/4 thromb, 4.5% G3 stomatitis	Symptomatic improvement dyspnea (68%), pain (33%)
Knuutila, 2000 (80)	MM, measurable or assessable, PS 0-2	Docetaxel 60mg/m ² + CPT-11 190mg/m ² q3w	15 entered 13 eval for resp 15 eval for tox	Epi 8 Sar 2 Mixed 3 Other 2	CR 0 PR 0 SD 3	0%	TTP 7mo	8.5mo	27% G3/4 neut, 47% (7 pts) G4 FN, 20% infection, 33% G3/4 N/V, 40% (6 pts) G3/4 diarrhea; trial d/c due to toxicity	NR
Gridelli, 1992 (81)	MM, PS 0-2, no prior CT or RT, measurable disease	Mit-C 10mg/m ² d1 + Vindesine 3mg/m ² d1-8 q4w	12 entered & eval	NR	CR 0 PR 0 SD 3	0%	NR	9.5mo	17% G3 leuk, 8% G3 neuro	NR

SUBTOTAL			117 entered 95 eval for resp		1/15 (CR/PR)	10.6 % (95% CI 4.9-16.3) ITT 9.4% (95% CI 4.4-14.3)			
TOTAL			247 entered 217 eval for resp (excluding single arm MTX)		3/33 (CR/PR)	11.7% (95% CI 7.6-15.7) ITT 10.4% (95% CI 6.8-14.1)	Range 6-13.5mo		

Notes: Adr – Adriamycin, CAMEO – cyclophosphamide+adriamycin+methotrexate+etoposide+vincristine, CI – confidence interval, CPT-11 – irinotecan, CR – complete response, CT – chemotherapy, Cy – cyclophosphamide, d – day(s), d/c – discontinued, derm – dermatological toxicity, Dx – doxorubicin, DRD – drug related deaths, Ep – epirubicin, Epi – epithelial, Etop – etoposide, eval – evaluable, FN – febrile neutropenia, G – grade, Gem – gemcitabine, G-CSF – granulocyte colony stimulating factor, GM-CSF – granulocyte-macrophage colony stimulating factor, Grp – group, HD – high dose, Ifos – ifosfamide, ITT – intention to treat, KPS – Karnofsky performance status, leuk – leukopenia, Mit-C – mitomycin C, MM – malignant mesothelioma (pleural or peritoneal), mo – month(s), MPM – malignant pleural mesothelioma, MTX – methotrexate, neuro – neurotoxicity, neut – neutropenia, NR – not reported, N/V – nausea/vomiting, Pem – pemetrexed, PFS – progression-free survival, PR – partial response, PS – performance status, pt – patient(s), q – every, resp – response, RT – radiotherapy, Sar – sarcomatous, SD – stable disease, thromb – thrombocytopenia, tox – toxicity, TTP – time to progression, VCR – vincristine, w – week(s).

Table A10. Non-comparative studies of single-agent platinum chemotherapy.

Author, Year (Reference)	Inclusion criteria	Intervention	Number of patients	Histology	Response	Response rate (ITT)	PFS/TTP	Median survival	Toxicity	Quality of Life
Cisplatin										
Planting, 1994 (82)	MM, stage II, PS 0-2, measurable disease	Cis 80mg/m ² weekly x 6	14 entered	NR	CR 0 PR 5 SD 7	ITT 36%	NR	NR	14% G3 neut, 70% G3/4 thromb, 2 (14%) G3 ototoxicity	NR
Rebattu, 1993 (83)	MM, no prior treatment in preceding month	Cis 200mg/m ² over 5d q4w	13 entered 12 eval (10 pleural, 3 peritoneal)	Epi 9 Sar 2 Mixed 2	CR 0 PR 3 SD 5	ITT 23%	NR	11mo	46% G3/4 N/V, 8% G3 leuk	No formal QOL; 5pts with pain had a dramatic subjective improvement
Zidar, 1988 (84)	MM, pleural (32), peritoneal (2), PS 0-4, prior CT or RT allowed, measurable disease	Cis 100mg/m ² q3w	35 entered & eval	NR	CR 0 PR 5 SD 11	14.3% (95% CI, 0.05-0.30)	NR	7.5mo	Not graded; no DRD, 20% severe N/V 8.6% ototoxicity 11.4% renal failure, 12 pts d/c treatment due to side effects	NR
Markman, 1986 (85)	MM, prior CT allowed	Cis 90 or 100mg/m ² intracavitary: intrapleural (8 pts) or intraperitoneal (13 pts) q3w	21 entered & eval (11 pleural, 13 peritoneal)	NR	CR 1 (IP grp) PR 9 (8 IP, 1 IPL) response criteria not described	48%	NR	12mo	Not well documented; no severe toxicities reported	NR
Mintzer, 1985 (86)	MM, KPS ≤50, prior CT or RT allowed, measurable or eval disease	Cis 120mg/m ² q4w x 2, then q6w	25 entered 24 eval	Epi 13 Sar 3 Mixed 7	CR 0 PR 3	12.5% ITT 12% (95% CI, 4-31)	NR	5mo	Not well documented; 1 d/c treatment due to peripheral neuropathy 1 case severe N/V	NR
SUBTOTAL			108 entered 106 eval		1/25 (CR/PR)	20.5% (95% CI 13.1-27.8) ITT 20.0% (95% CI 12.8-27.2)				
Carboplatin										
Raghavan, 1990 (87)	MM, measurable or eval disease, prior CT allowed, PS 0-3	Cb 150mg/m ² d1-3 q4w	31 entered	NR	CR 1 PR 4 SD 8	16%	NR	8mo	13% G3 N/V, 3% G3 anemia, 6% G3 neut, 6% G4 thromb	NR

Vogelzang, 1990 (88)	MM, measurable and evaluable disease, PS 0-2, no prior CT, prior RT allowed	Cb 400mg/m ² q4w	41 entered 40 eval	Epi ^a 18 20 Sar ^a 5 4 Mixed ^a 4 0 Other ^a 2 4	CR 0 PR 3 SD 19	7%	FFS 2.8mo	7.1mo	No deaths, 6% G3/4 leuk, 25% G3/4 anemia, 4% FN, 28% G3/4 N/V	NR
Mbidde, 1986 (89)	MM, prior CT or RT allowed	Cb 400mg/m ² (10pts)q4w Cb 300mg/ m ² (7pts) q4w	17 entered & eval (13 pleural, 4 peritoneal)	NR	CR 1 PR 1	12%	NR	NR	6% G3/4 N/V, 6% G3 leuk	NR; 4 pts achieved symptomatic benefit (does not define how this was determined)
SUBTOTAL			89 entered 88 eval		2/8	10.3% (95% CI 4.0-16.6) ITT 10.1% (95% CI 3.9-16.3)				
Experimental Platinum Analogues										
Giaccone, 2002 (90)	MPM, measurable disease, pts had relapsed or had progressive disease after prior CT, PS 0-2	150mg/m ² of platinum analogue ZD0473 d1 q3w x 2 minimum (The first 14 pts received a starting dose of 120mg/m ² with 6 of these receiving an escalated dose of 150mg/m ²)	47 entered 43 eval	NR	CR 0 PR 0 SD 24	0%	Median TTP 2.5mo (95% CI, 1.4-3.4mo)	6.7mo (95% CI, 5.4-9.1mo)	8.5% G3/4 anemia, 19.1% G3/4 neut, 21.2% G3/4 leuk, 36.3% G3/4 thromb	QOL was assessed using the FACT-L questionnaire and the LCS: No change in pts' QOL throughout the trial (Median scores did not change significantly)
SUBTOTAL			47 entered 43 eval for resp		0/0 (CR/PR)	0%		6.7mo		
TOTAL (Excluding experimental platinum analogues)			197 entered 194 eval for resp		3/33 (CR/PR)	14.6% (95% CI 9.8-19.4) ITT 14.3% (95% CI 9.6-19.0)		Range 5-12mo		

Notes: Cb – carboplatin, CI – confidence interval, Cis – cisplatin, CR – complete response, CT – chemotherapy, d – day(s), d/c – discontinued, DRD – drug related deaths, Epi – epithelial, eval – evaluable, FACT-L – Functional Assessment of Cancer Therapy-Lung, FFS – failure-free survival, FN – febrile neutropenia, G – grade, grp – group, IP – intraperitoneal, IPL – intrapleural, ITT – intention to treat, KPS – Karnofsky performance status, LCS – lung cancer subscale, leuk – leukopenia, MM – malignant mesothelioma (pleural or peritoneal), mo – month(s), MPM – malignant pleural mesothelioma, neut – neutropenia, NR – not reported, N/V – nausea/vomiting, PFS – progression-free survival, PR – partial response, PS – performance status, pts – patient(s), q – every, QOL – quality of life, resp – response, RT radiotherapy, Sar – sarcomatous, SD – stable disease, thromb – thrombocytopenia, TTP – time to progression, w – week(s).

^a – Assessed by two pathologists.

Table A11. Non-comparative studies of platinum-based combination chemotherapy.

Author, Year (Reference)	Inclusion criteria	Intervention	Number of patients	Histology	Response	Response rate	PFS/TTP	Overall Median survival	Toxicity	Quality of Life
Hillerdal, 2003 (91) abstract	MPM, PS 0-2, previously untreated, stage I-IV	Pegylated liposomal Dx 30mg/m ² + Cb 5AUC d1 and Gem 1000mg/m ² d1,8 q3w x 6	47 entered & eval	NR	CR 1 PR 17	38%	NR	NR	NR, however, hematological toxicity was reported as fairly high.	NR
Pennucci, 1997 (92)	MM, PS 0-2, measurable or evaluable disease, stage II-IV, symptomatic	Cis 60mg/m ² + Dx 60mg/m ² + Mit-C 10mg/m ² q4w x 6	24 entered 23 eval for resp 24 eval for tox	Epi 18 Sar 2 Mixed 4	CR 0 PR 5 SD 9	ITT 21%	NR	10.5mo	12% G3/4 leuk, 12% G3/4 thromb, 4% G3 anemia	Symptoms better in all pts with PR and 2 SD
Tomiak, 1997 (93) Abstract	MM, unresectable	Cis 30mg/m ² d1-4 + Ep 90mg/m ² d4 q3w	9 entered & eval	NR	CR 0 PR 3 SD 5	33%	NR	14mo	1 death, 77% G3/4 N/V, 33% G3/4 thromb, 33% FN; 1 pt d/c tx due to tox	NR
Shin, 1995 (94)	MM, PS 0-2, measurable or evaluable disease, 2 pts prior CT	Cy 500 mg/m ² + Dx 50 mg/m ² + Cis 80 mg/m ² q3w, then Cis dose reduced to 50 mg/m ² for subsequent cycles	23 entered & eval (note competing study)	Epi 14 Sar 4 Mixed 1 Other 4	CR 0 PR 7	ITT 30%	NR	13.9mo	No toxic deaths; 76% G3/4 neut, 13% G3/4 N/V, 4% G3 diarrhea, 9% G3/4 infection, 1 pt CHF	NR
Breau, 1993 (95)	MPM	Cis 20mg/m ² d1-5 + Dx 15mg/m ² d1-5 + BI 3mg/m ² d1-5 + Mit-C 1mg/m ² d1-5 q3w x10(max) + hyaluronidase: 1) intrapleurally 2,000-5,000 units/injection, 2-3 injections/week as long as pleural cavity remained open 2) subcutaneously 5,000-10,000 units/d	27 entered & eval	Epi 22 Fusiform 2 Mixed 3	CR 2 PR 10 SD 10	ITT 44.4%	Median TTP: CR 12.5mo PR 13mo	15mo	6% G3/4 N/V 11/133 courses G3/4 leuk Renal toxicity, 1 pt; Interstitial pneumonia, 2 pts; Cardiomyopathy, 1pt	No formal QOL assessment; improvement in respiratory symptoms and general health in all responders and 6 pts with SD

Ardizzoni, 1991 (96)	MM, measurable and eval disease, no prior CT, symptomatic	Cis 60mg/m ² + Dx 60mg/m ² q3w	26 entered 24 eval	Epi 5 Mixed 6 Other 15	CR 0 PR 6 SD 8	25% ITT 23%	NR	10mo	No deaths; 35% G3/4 N/V, 5% neuro	Assessed symptoms and PS; 50% (12/ 24) clinical improvement ; 33% improvement in dyspnea, 56% pain reduction
Henss, 1988 (97)	MM, no prior CT, KPS ≤70, measurable or eval disease	Cis 60mg/m ² d1,2 + Dx 40mg/m ² d3 q4w	19 entered & eval	NR	CR 2 PR 6	ITT 42%	NR	12mo	32% G3 leuk, 21% G3 GI tox, 5% (1 pt) G4 renal failure	NR
SUBTOTAL			175 entered 172 eval		5/54 (CR/PR)	33.3% (95% CI 26.3-40.2) ITT 32.4% (95% CI 25.6-39.2)				
Bakhshandeh, 2003 (98)	MPM, PS 0-2	Whole body hyperthermia with: Ifosfamide 5g/m ² @ 37°C d1 + Cb 300mg/m ² @ 41.8°C d1 + Etop 150mg/m ² d2,3 q4w x 3	27 entered 25 eval	Epi 16 Sar 2 Mixed 7	CR 0 PR 5 SD 14	20% (95% CI, 8.9-39.1%) ITT 18.5%	Median PFS 6.8mo (95% CI, 5.6 - 8.0mo)	17.7mo (95% CI, 15-20.3mo)	74% G3/4 neut, 33% G3/4 leuk, 10% G3/4 anemia, 9% G3 nausea, 5% G3 infection, 4% G3 vomiting	NR
Planting, 1995 (99)	MM, stage II, PS 0-2, no prior CT	Cis 70mg/m ² d1,8,15, and d29,36,43 + oral Etop 50mg d1-15 and d29-43. Then maintenance oral Etop d 1-21q4w	25 entered & eval	NR	CR 1 PR 5 SD 12	ITT 24%	NR	Overall median survival not reported	28% G3/4 leuk, 12% G3/4 anemia, 32% G3/4 N/V, 4% G4 thromb	NR
Eisenhauer, 1988 (100)	MM, no prior CT, PS 0-2, measurable disease	Cis 25mg/m ² + Etop (V-16) 100mg/m ² IV d1-3 q3w	30 entered 26 eval (26 pleural, 1 peritoneal, 3 ineligible)	Epi 13 Sar 4 Mixed 6 Other 4	CR 0 PR 3	11.5% ITT 10%	NR	NR	8% G3 anemia, 8% G3 N/V, 4% G3 malaise	NR

SUBTOTAL			82 entered 76 eval		1/13 (CR/PR)	17.1% (95% CI 8.7-25.4) ITT 15.3% (95% CI 7.6-23.0)				
Middleton, 1998 (101)	MM, PS 0-3, 2 pts prior tamoxifen, symptomatic	Mit-C 8mg/m ² d1 q6w + Vb 6mg/m ² d1 + Cis 50mg/m ² q3w	39 entered 39 eval for resp 37 eval for tox	NR	CR 0 PR 8 SD 26	ITT 20.5%	NR	6mo	3% G3 anemia, 14% G3/4 leuk, 3% G3 thromb, 5% G3 infection, 8% G3 N/V,	62% (24/39) had improved symptoms (pain, dyspnea, malaise, cough); 8/8 pts with PR improved
Tsavaris, 1994 (102)	MM, measurable disease, KPS ≥70, prior CT allowed; no prior RT	Cis 100mg/m ² d1 + Vb 6mg/m ² d1,8 q4w	20 entered & eval	Epi 13 Sar 3 Mixed 4	CR 1 PR 4 SD 9	ITT 25%	Mean TTP 5.2mo	NR	No DRD; 20% G3 N/V	NR
SUBTOTAL			59 entered & eval		1/12 (CR/PR)	21.9% (95% CI 11.4-32.4) ITT 21.9% (95% CI 11.4-32.4)				
Castagneto, 2003 (103) abstract	MPM, PS 0-2, measurable disease	Gem 1250mg/m ² d1,8 + Cis 75mg/m ² d2, q3w x 6	35 entered & eval	Epi 22 Sar 3 Mixed 10	CR 0 PR 9 SD 14	26% ITT 26%	Media n PFS 8mo	13mo	35% G3 N/V, 23.5% G3-4 hematological toxicity	NR
Favaretto, 2003 (104)	MPM, PS 0-2, measurable disease, no prior CT or RT	Cb 5AUC d1 + Gem 1000mg/m ² d1,8,15 q4w x 6 13 pts had decortication, with 6 of these receiving intraoperative CT	50 entered & eval	Epi 34 Sar 3 Mixed 13	CR 0 PR 13 SD 25	26% (95% CI, 15- 40%) ITT 26% (95% CI, 15- 40%)	Media n PFS 9.2mo	15.2mo	15% G3/4 thromb, 11% G3/4 leuk, 5% G3 anemia	No formal assessment of QOL: Dyspnea improved in 46% of pts; pain decreased in 26% of pts

Pinto, 2003 (105) abstract	MPM, no prior treatment	Cis 75mg/m ² d1 + Gem 1200mg/m ² d1,8 q3w x 4 followed by mitoxantrone 10mg/m ² d1 + methotrexate 35mg/m ² d1 + Mit-C 7mg/m ² d1 q3w x4 with Mit-C in alternate cycles	53 entered 35 eval	Epi 42 Sar 1 Mixed 9 Unknown 1	CR 1 PR 9 SD 20	28.6% ITT 18.9%	Median TTP 8mo	NR With median follow-up of 14 mo, 71.7% of patients still alive	Cis-Gem: 17.8% G3/4 neut, 10.7%G3/4 thromb, 7.1% G3/4 vomiting Mitoxantrone/ Mitotrexate/Mit-C: 28.5% G3/4 neut, 7.1% G3/4 anemia, 10.7%G3/4 thromb	60% had improvement in dyspnea, 66.7% had improvement in pain
Nowak, 2002 (106)	MPM, PS 0-2, measurable disease, no prior CT for MM, no prior RT	Cis 100mg/m ² d1 + Gem 1000mg/m ² d1,8,15 q4w x 6	55 entered 53 eval	Epi 42 Sar 7 Mixed 2 Unknown 2	CR 0 PR 17 SD 31	33% (95% CI,20-46%) ITT 31%	Median TTP 6.4mo	11.2mo	49% G3/4 thromb, 56% G3/4 neut, 36% G3/4 leuk, 7% G3 anemia, 20% G3 nausea, 17% G3 vomiting, 13% G3 neuro, 4% G3 infection, 2% G3 diarrhea	Those that responded improved on the EORTC-QLQ-C30 global QOL scale compared to non-responders (p=0.006), however effect did not persist past cessation of CT
Steele, 2002 (107) abstract	MPM, PS 0-2, no prior treatment	Cis 40mg/m ² + Irinotecan 100mg/m ² q2w + Mit-C 6mg/m ² q4w x 6	22 entered 18 eval	Epi 15 Sar 5 Mixed 2	CR 0 PR 9 SD 6	ITT 41%	NR	Not yet reached at median follow-up 8.8mo	61% G3 neut 6% G4 neut, 7% G3 diarrhea	NR
Byrne, 1999 (108)	MM, PS 0-2, measurable disease, no prior CT, symptomatic	Cis 100mg/m ² d1 + Gem 1000mg/m ² d 1,8,15 q4w x 6	21 entered 20 eval	Epi 13 Sar 0 Mixed 8	CR 0 PR 10 SD 9	ITT 48%	PFS 5.8mo (95% CI 3.9-7.6mo)	9.5m (95%CI 5.5-13.6mo)	38% G3 leuk, 33% G3/4 thromb, 33% G3 N/V, 5% (1pt) FN, no deaths	No formal assessment of QOL; 9/10 PR + 3/9 SD had improved symptoms

Kasseyet, 1999 (109)	MM, KPS ≤70, stage II disease, measurable or eval disease, no prior CT	Cis 60mg/m ² d1+ FA 100mg/m ² d1-4 + FU 600mg/m ² d1-4 + Mit-C 10mg/m ² d3 +Etop 100mg/m ² d1-3 + G-CSF q4w x 4	50 entered 45 eval for resp	Epi 33 Sar 6 Mixed 3 Other 3	CR 0 PR 17 SD 18	38% ITT 34%	NR	16mo	11% pneumonitis, 29% G3/4 leuk, 31% G3/4 neut, 16% G3/4 thromb, 16% G3 anemia	21 (47%) clinical benefit (less pain and dyspnea)
Nakano, 1999 (110)	MM, PS 0-2, measurable or eval disease, no prior CT	CPT-11 60mg/m ² d1,8 15, + d1 Cis 60mg/m ² q4w	15 entered & eval	Epi 10 Sar 1 Mixed 4	CR 0 PR 4 SD 10	ITT 27%	TTF 5.1mo	6.5mo	20% G3 leuk, 13% G3 anemia	NR
Samuels, 1998 (111)	MM, unresectable, measurable or evaluable disease, PS 0-2, no prior CT or RT	Dihydroazacytidine 1500mg/m ² /24h x 120h + Cis 15mg/m ² d1-5, q3w	36 entered 26 eval for resp	Epi 22 Sar 7 Mixed 7	CR 0 PR 5 SD 15	19% ITT 14%	TTF 2.7mo	6.4mo	29% G3/4 gran, 3% G3 thromb, 3% G3 anemia, 14% G3/4 chest pain, 6% G3/4 dysrhythmia, 12% G3/4 thrombosis, 9% G3 nausea, 2 early deaths	NR
SUBTOTAL			337 entered 297 eval		1/93 (CR/PR)	30.6% (95% CI 25.5-35.8) ITT 26.1% (95% CI 21.5-30.7)				
Fizazi, 2003 (112)	MM, PS 0-2, prior CT allowed	Oxaliplatin 130mg/m ² d1 + Ral 3mg/m ² d1 q3w	72 entered 70 eval for resp 72 eval for tox	Epi 46 Sar 3 Mixed 12 Other 8 Missing 1	CR 0 PR 14 SD 32	24.6% (95% CI, 14.1-37.8) ITT 20% (95% CI, 11.4-31.3)	TTP 4.1mo (95% CI, 3.0-5.1mo)	7.4mo (95% CI, 5.5-9.2mo)	8% G3/4 neuro, 8% G3/4 N/V, 8% G3/4 leuk, 4% G3/4 anemia, 4% G3/4 diarrhea	Symptom response rates: 23% normal activity, 20% asthemia, 30% pain, 36% SOB, 21% appetite
Schuetz 2002 (113)	MPM, measurable disease, no prior CT, PS 0-2, life expectancy ≥12w	Oxaliplatin 80mg/m ² d1,8 + Gem 1000mg/m ² q3w x6	25 entered & eval	Epi 16 Sar 1 Mixed 8	CR 0 PR 10 SD 6	ITT 40% (95% CI, 21-45)	TTP 7mo	13mo	5% G 3/4 neuro, 70% myalgia, 15% nausea	NR

Steele, 2001 (114) abstract	MM	Oxaliplatin 130mg/m ² d1 + VNR 30mg/m ² d18 q3w	26 entered and eval	Epi 13 Sar 5 Mixed 7 Other 1	CR 0 PR 6 SD 17	ITT 23%	NR	Not reached	18% G3/4 neut, 12% G3/4 N/V, 12% G3/4 malaise, 12% G3/4 anorexia	Rotterdam; to be analyzed at trial completion
SUBTOTAL			123 entered 121 eval		0/30 (CR/PR)	23.7% (95% CI 16.2-31.2) ITT 23.2% (95% CI 15.9-30.6)				
Aitini, 1994 (115)	MM, PS 0-2, prior treatment allowed	IP Cis 100mg/m ² + Ara-C100mg weekly x 3 q9w	7 MM entered 6 eval (33 in whole study)	NR	CR 3 PR 1	ITT 57%	NR	NR	Not documented	NR
Bednar, 1999 (116) abstract	MM, prior CT allowed	Cb AUC 5 + Paclitaxel 175mg/m ² q4w	7 entered & eval	Epi 6 Sar 1	CR 1 PR 0 SD 2	ITT 14%	NR	12mo	29% (2pts) G3 leuk	NR
TOTAL			790 entered 738 eval		12/203 (CR/PR)	27.3% (95% CI 24.1-30.4) ITT 24.9% (95% CI 22.0-27.9)		Range 6-17.7mo		

Notes: Ara-C – cytosine arabinoside, AUC – area under the curve, BI – bleomycin, Cb – carboplatin, Cis – cisplatin, CHF – congestive heart failure, CPT-11 – irinotecan, CR – complete response, CT – chemotherapy, Cy – cyclophosphamide, d – day(s), d/c – discontinued, DRD – drug-related deaths, Dx – doxorubicin, Ep – epirubicin, Epi – epithelial, EORTC – European Organization for Research and Treatment of Cancer, Etop – etoposide, eval – evaluable, FA – folinic acid, FN – febrile neutropenia, FU – 5-fluorouracil, G-CSF – granulocyte colony-stimulating factor, Gem – gemcitabine, gran – granulocytopenia, IP – intrapleural, ITT – intention to treat, IV – intravenous, KPS – Karnofsky performance status, leuk – leukopenia, Mit-C – mitomycin C, MM – malignant mesothelioma (pleural or peritoneal), mo – month(s), MPM – malignant pleural mesothelioma, neuro – neurotoxicity, neut – neutropenia, NR – not reported, N/V – nausea/vomiting, op – operative, PFS – progression-free survival, PR – partial response, PS – performance status, pt – patient(s), q – every, QOL – quality of life, Ral – raltitrexed, RT – radiotherapy, Sar – sarcomatous, SD – stable disease, SOB – shortness of breath, sx – surgery, thromb – thrombocytopenia, tox – toxicity, TTF – time to treatment failure, TTP – time to progression, tx – treatment, Vb – vinblastine, VNR – vinorelbine, w – week(s).

Table A12. Non-comparative studies of chemotherapy in combination with immunotherapy.

Author, Year (Reference)	Inclusion criteria	Intervention	Number of patients	Histology	Response	Response rate (ITT)	PFS /TTP	Median survival	Toxicity	Quality of Life
Non-platinum-based chemotherapy										
Halme, 1999 (117)	MM, no prior CT or RT, PS 0-1, measurable disease	MTX 3g + FA rescue q2wx6 + IFN α 3x10 ⁶ d2-10 + IFN γ 50 μ g/m ² d 2,6,10	26 entered 24 eval	Epi 17 Sar 1 Mixed 8	CR 0 PR 7 SD 14	29% (95% CI, 13-51) ITT 27%	NR	17mo	27% G3 leuk, 12% G3 GI, 4% G4 neuro	NR
Bretti, 1998 (118)	MM, stage >1, PS 0-2, measurable disease, no prior CT or RT	Ep 10mg/m ² d1 + IL2 9x10 ⁶ d8-12, d15-19 q3w	21 entered & eval for resp 20 eval for tox	Epi 12 Sar 4 Mixed 1 Other 4	CR 0 PR 1 SD 7	5% (95% CI, 0-26) ITT 5%	PFS 5mo	10mo	10% G3 asthenia, 20% G3 fever, 15% G3 N/V, 15% G3/4 hem tox, 1 death from infection, 5% G3 diarrhea	NR
Upham, 1993 (119)	MM, measurable disease, PS 0-2, no previous CT, RT or IFN	IFN α -2a 9x10 ⁶ daily + Dx 25mg/m ² weekly x 12 w	25 entered & eval	NR	CR 0 PR 4 SD 11	ITT 16%	NR	11mo	60% G3/4 leuk (1 G4), 8% G3 anemia, 24% G3 N/V, 8% G3 mucositis, 2 bacterial pneumonia, 1 GM-septicemia	NR
SUBTOTAL			72 entered 70 eval for resp		0/12 (CR/PR)	11.2% (95% CI 4.1-18.3) ITT 11.2% (95% CI 4.2-18.2)				
Single-agent platinum chemotherapy										
O'Reilly, 1999, (120)	MM, unresectable, no prior CT or immunotherapy, prior RT allowed, measurable or assessable disease, KPS>60%	Cb 150mg/m ² d1-3 q4w + IFN α -2a 3x10 ⁶ daily	15 entered 14 eval for resp 15 eval for tox	Epi 11 Sar 4	CR 0 PR 1 SD 3	ITT 7% (95 % CI, 0-20)	TTP 14w	25w	13% G3/4 asthenia, 13% G3/4 anemia, 7% G3/4 neut, 7% G3/4 plt, 1 fatal pul hemorrhage due to progressive disease	NR
Purohit, 1998 (121)	MM, measurable disease, PS 0-2, stage >1, no prior treatment	Cis 60mg/m ² d2 q1w + IFN α -2a 6 x10 ⁶ d1-4 q1w x 4, q8w x 2 cycles, then 3w cycles for total of 25w	13 entered 12 eval for resp 13 eval for tox	Epi 11 Sar 1 Mixed 1	CR 1 PR 4 SD 6	42% ITT 38%	6.4mo	16.5mo	38% G3 anemia, 23% G3/4 plt, 38% G3/4 neut, 31% G3 GI, 31% G3 asthenia	NR; 6 patients improved symptoms (chest pain 5/7, dyspnea 4/7)

Trandafir, 1997 (122)	MPM, no prior CT or immunotherapy, PS 0-2, bidimensionally measurable or eval	Cis 60mg/m ² d2 + IFN α 6x10 ⁶ d1-4 weekly x 4 q8w for 2 cycles, then x 3 q6w	33 entered 30 eval	Epi 17 Mixed 10 Fusiform 1 Other 2	CR 1 PR 7 SD 13	27% ITT 24%	TTF 7mo	15mo	53% G3/4 N/V, 13% G3 neuro, 27% G3 neut, 30% G3/4 plts, 100% >G2 asthenia	NR
Soulie, 1996 (123)	MM, measurable disease, PS 0-2, no prior CT or RT	Cis 60mg/m ² d2 + IFN 3x10 ⁶ d1-4 weekly x 5 q8w ^a	29 entered 25 eval for resp 26 eval for tox	Epi 14 Sar 3 Mixed 9	CR 0 PR 10 SD 4	40% ITT 34%	Med PFS 6moT TP 11mo	12mo	^b 27% G3/4 neut, 12% G3/4 plt, 8% G3/4 neuro, 38% G3/4 N/V, 27% G3/4 weight loss (>10%)	NR; 54% had decrease \geq 1 point in WHO PS
Pass, 1995 (124)	MM, inoperable, measurable disease, PS 0-2, prior CT or RT allowed, no prior immunotherapy	Cis 25mg/m ² d8,15,22,29 + Tamoxifen 20mg po BID d1-35 + IFN α -2a 3x /w	39 entered 36 eval	Epi 25 Sar 5 Mixed 6	CR 0 PR 7 SD 17	19% ITT 18%	NR	8.7mo	1 death due to myocardial infarction after interferon administration, tox not clearly documented	NR
SUBTOTAL			129 entered 117 eval for resp		2/29 (CR/PR)	21.8% (95% CI 14.6-29.0) ITT 19.9% (95% CI 13.2-26.5)				
Combination platinum-based chemotherapy										
Parra, 2001 (125)	MPM, PS 0-2, no prior CT, bidimensionally measurable disease	Cis 60mg/m ² d1 + Dx 60mg/m ² d1 q4w, IFN α -2b 3x10 ⁶ 3 x w	37 entered 35 eval for resp 34 eval for tox	Epi 19 Sar 4 Mixed 6 Other 6	CR 0 PR 10 SD 11	29% (95% CI, 15-45) ITT 27%	NR	9.3mo	38% G4 neut, 24% G3/4 plt, 3% FN, 32% G3 fatigue, 30% G3/4 anemia, 76% G3/4 leuk, 9% G3 fever	NR
Metintas, 1999 (126)	MPM, KPS \leq 50, bidimensionally measurable disease, no prior CT, RT, or Sx	Cis 30mg/m ² d1,2 + Mit-C 8mg/m ² d1 + IFN 2 α 4.5 x 10 ⁶ twice weekly q4w	55 entered (12 inadequate F/U) 43 eval	Epi 24 Sar 6 Mixed 8 Other 5	CR 2 PR 8 SD 17	23% ITT 18%	TTP 8mo (\pm 0.5 mo)	11.5mo	No treatment deaths, 5% G3 neut, 2% G3 anemia, 23% G3 N/V 1 pul edema 1 encephalopathy 1 Mit-C induced pneumonitis	NR

Hasturk, 1996 (127)	MM, pleurectomy, PS 0-2, stage I/II	Cis 50mg/m ² q3w + Mit-C 10mg /m ² q6w + IFN 10x 10 ⁶ IV q3w immediately prior to Cis + IFN 10x 10 ⁶ im q3w 4hrs prior to Cis	23 entered (3 excluded due to rapid deterioration) 20 eval	Epi 16 Mixed 4	CR 0 PR 0 SD15	0%	NR	12mo	No G3/4 tox G2 leuk 10%, G2 N/V 15%	Not formally assessed although pts with SD had improved QOL, PS, and symptom relief
Tansan, 1994 (128)	Symptomatic MM, no prior CT, prior RT allowed, measurable or evaluable disease, PS 0-2,	Cis 50mg/m ² d1 q3w + Mit-C 10mg/m ² q42d + IFN α -2b 20x10 ⁶ iv q3w + IFN α -2b 10x10 ⁶ im q3w	20 entered 19 eval	Epi 20	CR 0 PR 2 SD 11	11% ITT 10%	NR	15mo	Not well documented; no toxic deaths, 63% G2/3 N/V, 16% G2/3 renal tox	NR
SUBTOTAL			135 entered 117 eval for resp		2/20 (CR/PR)	10.2% (95% CI 5.1-15.2) ITT 8.8% (95% CI 4.3-13.2)				
TOTAL			336 entered 304 eval for resp		4/61 (CR/PR)	13.3% (95% CI 9.7-16.9) ITT 12.0% (95% CI 8.7-15.3)		Range 6.2-17mo		

Notes: BID – twice daily, Cb – carboplatin, CI – confidence interval, Cis - cisplatin, CR – complete response, CT – chemotherapy, d – day(s), Dx – doxorubicin, Ep – epirubicin, Epi – epithelial, eval – evaluable, FA – calcium folinate, FN – febrile neutropenia, F/U – follow-up, G – grade, GI – gastrointestinal toxicity, GM- – gram negative, hem – hematologic, hrs – hours, IFN – interferon, IL2 – interleukin-2, im – intramuscularly, ITT – intention to treat, IV – intravenous, KPS – Karnofsky performance status, leuk – leukopenia, Mit-C – mitomycin C, MM – malignant mesothelioma (pleural or peritoneal), mo – month(s), MPM – malignant pleural mesothelioma, MTX – methotrexate, neuro – neurotoxicity, neut – neutropenia, NR – not reported, N/V – nausea/vomiting, PFS – progression-free survival, plt – platelet(s), PR – partial response, PS – performance status, pul – pulmonary, q – every, QOL – quality of life, resp – response, RT – radiotherapy, Sar – sarcomatous, SD – stable disease, Sx – surgery, tox – toxicity, TTP – time to progression, w – week(s), WHO – World Health Organization.

^a – 12 pts received treatment 5w on, 3w off; remaining received 4w on, 4w off; dose lowered due to increasing emesis and fatigue.

^b – Toxicity more severe in higher dose group and related to cycle duration.



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Evidence-based Series #7-14-1: Section 3

The Use of Chemotherapy in Patients with Advanced Malignant Pleural Mesothelioma: Guideline Development and External Review - Methods and Results

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A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: October 12, 2004

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline.* This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.

- *Section 3: Guideline Development and External Review: Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Lung DSG of Cancer Care Ontario's PEBC. The series is a convenient and up-to-date source of the best available evidence on the use of chemotherapy in patients with MPM, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Disease Site Group Consensus Process

No identified trials directly answered the question of whether chemotherapy improves survival or QOL for patients with MPM compared with BSC. Weak evidence from several of the phase II trials existed to show that chemotherapy produced symptom improvement in some patients with MPM. Additionally, data from one large randomized trial showed improved survival and QOL for combination compared with single-agent chemotherapy. Therefore, the consensus of the Lung DSG was that there was sufficient evidence to support the use of combination chemotherapy with cisplatin and pemetrexed for patients with symptomatic MPM who have good performance status (ECOG 0-1). Vitamin supplementation with vitamin B₁₂ and folic acid is an essential component of chemotherapy treatment with pemetrexed and cisplatin as supplementation substantially improves the toxicity profile of the chemotherapy regimen.

External Review by Ontario Clinicians

Following review and discussion of sections 1 and 2 of this evidence-based series, the Lung DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

<p>BOX 1: DRAFT RECOMMENDATIONS (approved for external review November 13 2003)</p>
<p><i>Target Population</i></p> <ul style="list-style-type: none"> • The opinions and recommendations apply to adult patients with symptomatic MPM who have a good performance status (ECOG 0-1) and are not suitable for surgical resection.
<p><i>Recommendations</i></p> <p>The lack of sufficient high quality evidence precludes definitive recommendations from being made. Instead, the Lung DSG offers the following opinions based on the evidence reviewed:</p> <ul style="list-style-type: none"> • There are no studies comparing chemotherapy to BSC for patients with MPM. • Combination chemotherapy with cisplatin and pemetrexed is associated with improved survival and QOL compared with single-agent cisplatin for patients with MPM. • There is sufficient evidence to support the use of cisplatin 75 mg/m² and pemetrexed 500 mg/m² given every three weeks. All patients should receive vitamin supplementation with vitamin B₁₂ 1000 µg monthly and folic acid 0.4-1.0 mg daily prior to starting the administration of pemetrexed and vitamin B₁₂ 1000 µg and folic acid 0.4-1.0 mg daily during the administration of pemetrexed.

- Patients should be encouraged to participate in clinical trials of treatment for mesothelioma.
- Carboplatin should not be routinely substituted for cisplatin.

Practitioner Feedback

A draft version of this report was reviewed by Ontario practitioners. Any changes made to the report as a result of practitioner feedback are described in the “Modifications/Actions” section below.

Methods

Practitioner feedback was obtained through a mailed survey of 141 practitioners in Ontario (35 medical oncologists, 22 radiation oncologists, 27 surgeons, and 57 respirologists). The survey consisted of items evaluating the methods, results, and interpretive summary. Written comments were invited. The practitioner feedback survey was mailed out on November 13, 2003. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Lung DSG reviewed the results of the survey.

Results

Fifty-nine responses were received out of the 141 surveys sent (42% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 35 indicated that the report was relevant to their clinical practice and they completed the survey. One respondent left that question blank but completed the survey and was included in the analysis below. Results of the practitioner feedback survey are summarized in Table 1.

Table 1. Results of the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing an evidence summary, as stated in the “Choice of Topic” section of the report, is clear.	34 (94)	1 (3)	1 (3)
There is a need for an evidence summary on this topic.	30 (83)	4 (11)	2 (6)
The literature search is relevant and complete in this evidence summary. ¹	33 (94)	2 (6)	0 (0)
I agree with the methodology used to summarize the evidence. ¹	32 (91)	3 (9)	0 (0)
I agree with the overall interpretation of the evidence in the evidence summary. ¹	28 (80)	6 (17)	1 (3)
The Opinions of the Disease Site Group section of this evidence summary is useful. ¹	27 (77)	6 (17)	2 (6)
An evidence summary of this type will be useful for clinical decision making. ²	21 (62)	9 (26)	4 (12)
At present, there is insufficient evidence to develop a practice guideline on this topic. ¹	19 (54)	10 (29)	6 (17)
There is a need to develop an evidence-based practice guideline on this topic when sufficient evidence becomes available. ²	26 (74)	7 (20)	1 (3)
Do you believe that there is sufficient evidence to use cisplatin and pemetrexed in patients with symptomatic malignant pleural mesothelioma in your own practice? ¹	Very likely or likely	Unsure	Not at all likely or unlikely
	25 (71)	6 (17)	4 (11)

¹ One practitioner did not respond to these questions.

² Two practitioners did not respond to these questions.

Summary of written comments

Twelve respondents (33%) provided written comments. The main points contained in the written comments were:

1. One practitioner responded that there is a need to compare chemotherapy to BSC. Although this respondent agreed that single-agent cisplatin is unlikely to negatively affect survival, he disagreed that it is unlikely to have little effect on QOL. Therefore, QOL studies should be carried out to determine if cisplatin (alone or in combination with pemetrexed) provides meaningful benefit to patients with malignant mesothelioma.
2. One practitioner responded that there is a need for an evidence-based practice guideline on this subject.
3. One respondent felt that undue weight was placed on only one good RCT, and therefore, the conclusions were premature. There is little data on QOL in mesothelioma patients treated with cisplatin alone—and that is all that is available in Canada. Also, response rates <20% to chemotherapy agents are always suspect, especially in a disease like mesothelioma where response is difficult to assess.
4. One respondent felt that cisplatin and pemetrexed is one option, but not the only option. Specifically, cisplatin and pemetrexed should not become the “standard regimen”. BSC is an option for many patients.
5. Two respondents questioned recommending a drug that is not available, and felt that recommendations should only be made for drugs that are available.
6. One practitioner questioned why surgical practice was not included (i.e., decortication/pleurectomy or extrapleural pneumonectomy plus chemotherapy).
7. One respondent felt that the inclusion of anecdotal reports (n<20) does not add any useful information to the report.
8. One respondent questioned whether a survival of 12.1 months compared to 9.3 months represented a clinically important benefit.
9. One respondent replied that there is no reason for this evidence summary to state that there has been only one good study in this disease.
10. One practitioner stated that the evidence summary was an excellent medical review of MPM, and that it highlights the obvious need for ongoing clinical trials to determine optimum therapy (supportive vs multimodal) for patients with this disease.
11. One respondent stated that MPM is uncommon and individual clinicians do not have much experience treating this disease. A national/international continuing medical education type of activity dealing with the impact of this disease would be of benefit.

Modifications/Actions

1. The authors of this evidence summary agree that there is a need for a comparison of chemotherapy to BSC. An ongoing phase III randomized trial comparing chemotherapy with active symptom control to active symptom control, alone, was identified. Results from this study will not be available for a number of years. However, the Lung DSG will incorporate results from this trial when they become available. Given the limited evidence currently available, the Lung DSG is only prepared to offer an opinion regarding the role of chemotherapy in the management of MPM at this time.
2. A systematic review forms the basis of this evidence summary. The systematic review was thorough and the Lung DSG feels that this evidence summary contains all available evidence regarding chemotherapy for the treatment of patients with MPM.
3. The Lung DSG has summarized all of the available evidence and found only one study of reasonable quality. Therefore the DSG’s opinions are supported by the available evidence. We acknowledge that it would be better to have a greater number of high-quality RCT’s available.

4. The Lung DSG disagrees with this comment and feels that the opinions expressed by the DSG are supported by the available evidence. We acknowledge that there are patients for whom chemotherapy is not an appropriate option.
5. The third question of the evidence summary was to find which agents have shown the highest response rates for MPM. Although pemetrexed was not yet available on the market in Canada at the time that practitioner feedback was undertaken, the drug was submitted to Health Canada and has been approved for use in Canada. Therefore, we feel it is appropriate to state that pemetrexed combined with cisplatin has the highest response rate of all chemotherapeutic agents.
6. This evidence summary focuses on the role of chemotherapy in MPM. The roles of surgery and radiation therapy are addressed in Evidence Summary Reports 7-14-2 and 7-14-3.
7. Trials with small patient samples ($n < 20$) were included only if they met the inclusion criteria. This evidence summary included all phase II and III data available on the subject. However, evidence from these trials was weighted appropriately, with more weight given to evidence from RCTs and to response rates from larger trials.
8. The magnitude of benefit is similar to that seen in other advanced malignancies where there have been documented clinical improvements associated with small improvements in survival.
9. The authors disagree with this comment as all but one of the RCTs were small and underpowered. Therefore more weight was given to the evidence documented in the trial reported by Vogelzang et al (10).
10. The authors agree that there is a need for ongoing clinical trials to determine the optimum therapy for patients with this disease.
11. The authors agree that MPM is uncommon and that individual clinicians do not have much experience treating this disease. We feel that the development of this evidence summary will assist clinicians in treating MPM.

Practice Guidelines Coordinating Committee Approval Process

The evidence summary report was circulated to 15 members of the PGCC for review and approval. Seven of 15 members of the PGCC returned ballots. One PGCC member is also a Lung DSG member and as such indicated on their ballot that they were not eligible to review the evidence summary report. Four PGCC members approved the evidence summary report as written. One member approved the evidence summary report with a comment for consideration by the Lung DSG. Another member approved the report conditional on the Lung DSG addressing specific concerns.

Summary of Comments

One PGCC member was concerned that the third “Key Evidence” bullet for the first “DSG Opinion” in the “Summary” section of the report convoluted the reasoning for the DSG’s opinion. The second PGCC member commented that the evidence summary report was very long and questioned whether there was a way to reduce the volume of information. The same member also questioned the feasibility of encouraging patients with a limited life span, dictated by the diagnosis, to participate in clinical trials of treatment for MPM.

Modifications/Actions

The Lung DSG agreed with the first member’s comment regarding the “Key Evidence” for the first “DSG Opinion”. The Lung DSG has rewritten this bullet in order to clarify the DSG’s position:

It is difficult to make judgements regarding the role of chemotherapy for MPM as there is no direct evidence comparing chemotherapy to BSC. The opinion of the Lung DSG is that single-agent cisplatin, used in one arm of the RCT reported by

Vogelzang et al [10], is unlikely to reduce survival in this patient population. Therefore, it is the opinion of the Lung DSG that there is sufficient indirect evidence from the above trial that pemetrexed and cisplatin combination chemotherapy improves survival and quality of life for patients with MPM.

The Lung DSG acknowledges the second PGCC member's comment that the evidence summary report is long and that it contains a large volume of information. However, much of this information is from small noncomparative phase II trials of chemotherapy for MPM. In order to reduce the volume of information contained within this evidence summary report, the Lung DSG would have to exclude all the phase II trials. The Lung DSG feels that those trials add important information regarding which chemotherapeutic agents have activity in MPM. Therefore, the Lung DSG feels that the evidence summary report must retain a large volume of information in order to address the evidence summary questions.

The Lung DSG does not agree with the second PGCC member's comment that questioned the feasibility of encouraging patients with MPM to participate in clinical trials given their limited life span. There are many diseases with similar survival in which patients are asked to join clinical trials. The Lung DSG has added a bullet to the 'Key Evidence' of the third 'DSG Opinion' in order to clarify why patients should participate in clinical trials of treatment for MPM.

The Lung DSG also received comments of an editorial nature that were incorporated into the evidence summary report.

Policy Review

This practice guideline report was submitted to the Policy Advisory Committee (PAC) for the October 2004 meeting, in order to obtain approval for the funding of pemetrexed and cisplatin combination therapy in the palliation of adult patients with advanced, symptomatic MPM with good performance status (ECOG 0-1) who are unsuitable for surgical resection. The combination of pemetrexed and cisplatin improves survival and quality of life in a disease for which there is currently no standard treatment. Vitamin supplementation with B₁₂ 1000 µg monthly and folic acid 0.4-1.0 mg daily should be started before the administration of pemetrexed and continued during treatment. A copy of this evidence-based series report, was requested by the Oncology Subcommittee of the Drug Quality and Therapeutics Committee of Ontario in December 2005 for raltitrexed and cisplatin for the treatment of patients with advanced, symptomatic malignant pleural mesothelioma who have a good performance status and are not suitable for surgical resection.

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