

ORIGINAL ARTICLE

Estimation of an optimal chemotherapy utilization rate for malignant pleural mesothelioma: An evidence-based benchmark for cancer care

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Abstract

Aims: Chemotherapy with cisplatin and pemetrexed has been shown to provide a survival benefit and improvement in quality of life in patients with malignant pleural mesothelioma (MPM). The reported chemotherapy utilization rates range from 18% to 61%. This study aimed to estimate the proportion of MPM patients that should receive chemotherapy based on best available evidence.

Methods: An optimal chemotherapy utilization model for MPM was constructed using indications for chemotherapy identified from evidence-based MPM treatment guidelines. Epidemiological data on the proportion of patients and their tumor-related attributes were combined with the chemotherapy indications to estimate the optimal chemotherapy utilization rate using decision analysis software (TreeAge Pro 2007). Sensitivity analyses were performed to assess the impact of major variations in the epidemiological data on the optimal chemotherapy utilization rate. The optimal rate was compared with the actual rate reported in the literature.

Results: Chemotherapy is recommended at least once during the disease trajectory in 65% of MPM patients. Sensitivity analyses indicate an optimal utilization rate ranging from 50% to 65%. This optimal rate is relatively comparable to the rates mentioned in contemporary reports from Canada (61% between 2003 and 2005) and Australia (54% between 2007 and 2009) and high when compared with data from the Netherlands (36% during 2005–2006).

Conclusion: An evidence-based model provided an optimal chemotherapy utilization rate of 65% for patients with MPM. Chemotherapy for MPM may be underutilized and barriers are likely multifactorial.

Key words: chemotherapy utilization rate, evidence-based medicine, malignant pleural mesothelioma, quality.

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a relatively uncommon but aggressive cancer arising from the

mesothelial surfaces of the pleural cavity.^{1,2} The symptom burden is often high and the disease is almost universally fatal. Evidence-based treatment approaches for MPM are limited, with chemotherapy being the only treatment modality proven to provide both a survival benefit^{3–5} and an improvement in quality of life (QoL) in randomized controlled trials.⁶ Published chemotherapy utilization rates for MPM range from 16% to 61%.^{7–13} However, no benchmark utilization rate has been established.

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The aims of this study were to estimate, based on the best available evidence, the optimal proportion of patients with MPM that should receive chemotherapy at least once during their disease trajectory and to compare this with actual chemotherapy utilization rates to determine if chemotherapy is underutilized in MPM.

METHODS

Indications for chemotherapy

A literature search for international clinical practice guidelines and phase III clinical trials was made to define the evidence-based indications for chemotherapy in MPM (Table 1).^{3–5,14–19} The parameters used in the PubMed search were deliberately broad and included “malignant pleural mesothelioma” and “chemotherapy” and “clinical trial” or “guideline”. The evidence in support of the indication for chemotherapy was ranked by the hierarchy of levels of evidence according to the Australian National Health and Medical Research Council (NHMRC).²⁰

Chemotherapy was considered to be the treatment of choice in clinical situations where it had been found to result in better clinical outcomes in comparison to other treatment modalities, best supportive care or no treatment. The superiority of chemotherapy could be based on survival advantage, improved QoL or toxicity profile. Chemotherapy could be recommended either alone or as part of a multimodality regimen such as in combination with radiotherapy and/or surgery.

Incidence data (tumor and patient attributes)

Data on the proportion of tumor and patient attributes for which chemotherapy is indicated were identified after a systematic review of the published literature and ranked using a previously described hierarchy (Table 2).²² Our group has used this method in a number of other studies estimating optimal chemotherapy utilization rates in other types of solid tumors.^{23–27} Where data were available from multiple sources, the attribute data with the highest ranked quality were used as the base value in the chemotherapy utilization tree.

Table 1 Indications for chemotherapy in malignant pleural mesothelioma – levels and sources of evidence

Outcome No. (as defined in Fig. 1)	Clinical scenario	Treatment indicated	Level of evidence [†]	References	Proportion of all patients
2	MPM, resectable, minimal comorbidities, good PS	Neoadjuvant chemotherapy	III	NCCN ¹⁴ BTS ¹⁵ ESMO ¹⁶ ERS/ESTS ¹⁷	0.02
4	MPM, resectable, minimal comorbidities, good PS	Adjuvant chemotherapy	III	NCCN ¹⁴ BTS ¹⁵ ESMO ¹⁶ ERS/ESTS ¹⁷	0.03
6	MPM, unresectable, minimal comorbidities, good PS	Palliative chemotherapy	I	NCCN ¹⁴ NCI PDQ ¹⁸ BCCA ¹⁹ CCO ⁵ BTS ¹⁵ ESMO ¹⁶ ERS/ESTS ¹⁷	0.60
Total proportion of patients in whom chemotherapy is recommended					0.65

[†]Levels of evidence for indications for chemotherapy: Level I – evidence obtained from a systematic review of all relevant randomized controlled trials; Level II – evidence obtained from at least one properly designed randomized controlled trial; Level III – evidence obtained from well-designed controlled trials without randomization – these include trials with “pseudo-randomization” where a flawed randomization method was used (e.g. Alternate allocation of treatments) or comparative studies with either comparative or historical controls; Level IV – evidence obtained from case series.²⁰ BCCA, British Columbia Cancer Agency; BTS, British Thoracic Society Standards of Care Committee; CCO, Cancer Care Ontario; ERS, European Respiratory Society; ESMO, European Society for Medical Oncology; ESTS, European Society of Thoracic Surgeons; MPM, malignant pleural mesothelioma; NCCN, National Comprehensive Cancer Network; NCI PDQ, National Cancer Institute Physicians Data Query; PS, performance status.

Table 2 The incidence of attributes used to define indications for chemotherapy in malignant pleural mesothelioma

Attribute	Proportion of populations with this attribute	Quality of information [†]	References
Good PS	0.65	λ	Chapman <i>et al.</i> ⁹
Resectable	0.09	ζ	Kao <i>et al.</i> ¹⁰
	0.06	γ	Flores <i>et al.</i> ²¹
Severe comorbidity	0.24	λ	Chapman <i>et al.</i> ⁹

[†]Hierarchy for epidemiological data:²² γ – epidemiological databases from other large international groups (e.g. US SEER); ζ – comprehensive single-institutional database; λ – single-institutional reports on selected groups of cases. AIHW, Australian Institute of Health and Welfare; MPM, malignant pleural mesothelioma; NSW, New South Wales; US SEER, United States Surveillance Epidemiology and End Results.

Estimation of the optimal chemotherapy utilization rate

The optimal chemotherapy utilization rate is defined as an evidence-based estimation of the proportion of patients with MPM who has an indication for chemotherapy based on guideline recommendations. The chemotherapy indication (Table 1) and incidence data for MPM (Table 2) were merged to generate an optimal chemotherapy utilization tree using TreeAge Pro 2007 software (TreeAge Software Inc. Williamstown, Massachusetts, USA). Each branch of the chemotherapy utilization tree represents an important tumor- or patient-related attribute that affects decision making regarding whether or not to offer chemotherapy. The terminal branches of the trees show whether or not chemotherapy is indicated for each of the clinical scenarios (see Fig. 1).

In the tree, each patient with an indication for chemotherapy treatment was only counted once (i.e. the tree was terminated at the point of chemotherapy being recommended) even if they developed other indications for chemotherapy during the course of their disease. The optimal utilization rate was calculated from the summation of the incidence of each indication for chemotherapy. This rate was then compared with actual chemotherapy utilization rates reported in the literature.

Sensitivity analysis

Sensitivity analysis was used to assess the effect of variation in epidemiological data. These variations occurred where data on patient and tumor attributes varied between sources by $\geq 10\%$.

RESULTS

Indications for chemotherapy

Based on guideline recommendations and the published literature,^{3–5,14–19} chemotherapy is indicated in the treatment of MPM in the following clinical situations (Table 1):

- Neoadjuvant/adjuvant chemotherapy for resectable disease.
- Palliative chemotherapy for advanced/unresectable disease.

A small, highly selected group of patients may have potentially resectable disease,^{10,21} but the role of radical surgical resection (i.e. extrapleural pneumonectomy [EPP]⁴) remains controversial.^{28,29} Observational studies suggest that EPP may confer a long-term survival benefit.^{14,15} The National Comprehensive Cancer Network (NCCN), British Thoracic Society (BTS), European Society of Medical Oncology (ESMO) and European Respiratory Society (ERS)/European Society of Thoracic Surgeons (ESTS) recommend a multimodality approach for patients being considered for radical surgery, with chemotherapy being given in either the neoadjuvant or the adjuvant setting.^{14–17}

All of the current guidelines recommend that palliative chemotherapy be considered for patients with MPM who have good performance status, as it has been shown to improve QoL and survival in patients with unresectable/advanced MPM.^{5,14–16,18,19}

Incidence data

The relevant tumor- and patient-related attributes determining the chemotherapy indication in MPM include resectability, patient performance status and patient comorbidities. The values used in the analysis were as stated in Table 2.

An Australian patterns of care study in MPM reported that the proportion of patients undergoing EPP was 9%.¹⁰ The United States (US) Surveillance, Epidemiology and End Results (SEER) population-based study, which included 5937 patients with MPM, showed that 6% of patients had radical surgery and total removal of the primary cancer site.²¹

Patients with poor performance status were not eligible for the initial phase III MPM clinical trials that demonstrated survival benefits^{3,4} and therefore patients

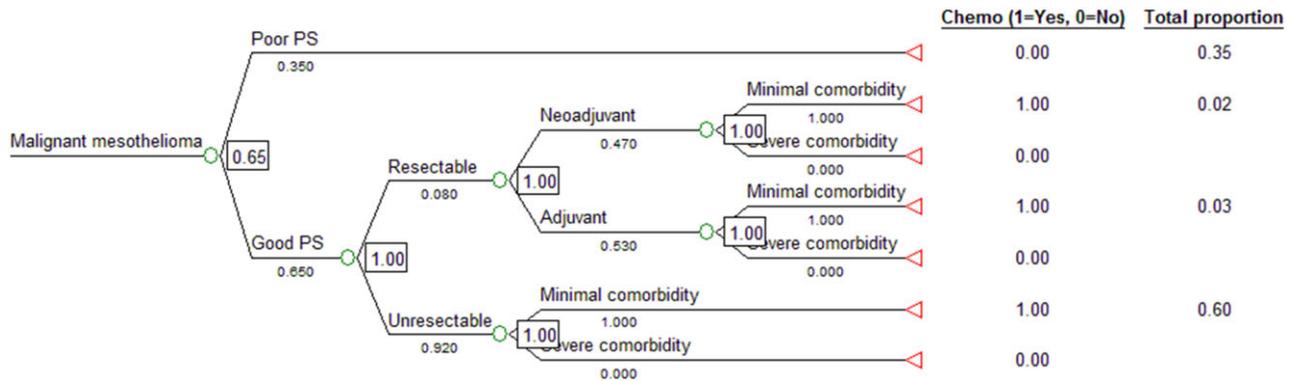


Figure 1 Optimal chemotherapy utilization tree for malignant pleural mesothelioma. Each branch of the chemotherapy utilization tree represents an attribute that affects the chemotherapy use decision. Each terminal branch of the tree shows whether or not chemotherapy is indicated. The description of the attributes is located above each branch of the tree with the proportion of that attribute located below that branch.

with an Eastern Cooperative Oncology Group (ECOG) performance status of >2 were considered unsuitable for chemotherapy. The proportion of MPM patients with performance status ECOG 0–2 was 65% in a small United Kingdom (UK) population-based study.⁹

MPM patients with severe comorbidities may not be eligible for chemotherapy treatment as the potential side effects may outweigh the benefits, but this was not an explicit exclusion criterion for the phase III MPM clinical trials.^{3,4} There are few data on the prevalence of severe comorbidity in patients with MPM. A population-based study from the UK reported that 24% of patients with MPM had severe comorbidities.⁹

Optimal chemotherapy utilization rate in MPM

Figure 1 demonstrates the optimal chemotherapy utilization tree for MPM. Chemotherapy is recommended at least once in the disease trajectory, according to the best available evidence, in 65% of all patients with MPM. Chemotherapy includes, but is not limited to, pemetrexed-based chemotherapy.

Sensitivity analysis

The variable data included for analysis were the proportion of patients with severe comorbidities (0–0.24).

Figure 2 is a tornado diagram demonstrating that the optimal proportion of MPM patients who should receive chemotherapy would fall from 65% to 50% if patients with severe comorbidities were excluded from receiving chemotherapy.

Tornado Diagram at Malignant Mesothelioma

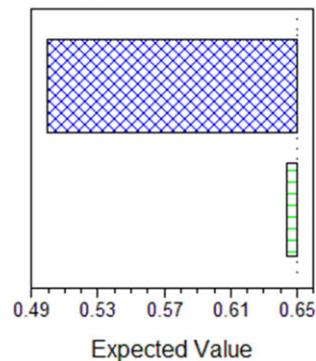


Figure 2 Tornado diagram showing sensitivity analysis of optimal chemotherapy utilization rates for malignant pleural mesothelioma. Blue shaded box represents proportion of patients with severe comorbidity in the unresectable branch of the tree. Green shaded box represents those in the resectable branch. This analysis showed that if patients who should receive chemotherapy would fall from 65% to 50%, patients with severe comorbidities were excluded from receiving chemotherapy in the model.

Comparison to actual chemotherapy utilization rates

The optimal chemotherapy utilization rate for MPM was compared with actual utilization rates reported in the literature (Table 3: rates presented chronologically). The actual utilization rate after the effectiveness of chemotherapy with cisplatin/pemetrexed was known (i.e. after 2003) tended to be higher compared with the rates

Table 3 Comparison of optimal and actual chemotherapy utilization rates for malignant pleural mesothelioma

	Year of survey	Chemotherapy utilization rate (%)
Optimal	Any time	63
Actual – USA (SEER) ⁷	1973–1984	37
Actual – Australia (NSW) ¹²	1980–1988	20
Actual – Germany ¹¹	1987–2000	16
Actual – The Netherlands ¹³	1995–1998	8
Actual – The Netherlands ¹³	2005–2006	36
Actual – Canada (BC) ⁸	1999–2002	31
Actual – Canada (BC) ⁸	2003–2005	61
Actual – UK (Leeds) ⁹	2002–2005	18
Actual – Australia (NSW) ¹⁰	2007–2009	54

BC, British Columbia; NSW, New South Wales; SEER, Surveillance Epidemiology and End Results.

before 2003 and was closer to the optimal rate of 65%. This included 61% in Canada and 54% in Australia. However, the actual rates in the UK (18% during the 2002–2005 period) and in the Netherlands (36% during the 2005–2006 period) were significantly lower than the optimal rate.

DISCUSSION

Our evidence-based model found that 65% of all MPM patients are eligible to receive chemotherapy. The strength of this model is that the methodology of estimation of optimal chemotherapy utilization has been validated and published in other solid tumors.^{23–27} Evidence-based treatment guidelines and the results of phase III clinical trials were used to identify the indications for chemotherapy in MPM. The complexities of clinical factors such as patient performance status and comorbidities that affect whether or not to offer chemotherapy were included in the model and the sensitivity analysis. Although controversy exists regarding whether radical surgery should be recommended for select MPM patients,^{28,29} there is consensus that it should be carried out in combination with chemotherapy.^{14–17}

Comparing our findings to the actual utilization rates reported in the literature, the utilization rates vary considerably between countries (16%–61%).^{7–13} Longitudinal chemotherapy utilization data also show an increase in chemotherapy utilization since 2003, when the survival advantage from modern chemotherapy regimens was published.³ This resulted in an increase in chemotherapy utilization rates from 20% to 54% in Australia,

from 8% to 36% in the Netherlands and from 31% to 61% in Canada.^{8,10,12,13} Therefore, the earlier rates published in the literature could not be directly compared with the optimal utilization rate,^{7,8,11–13} given that the model was constructed based on modern chemotherapy trials,^{3,4} and therefore may represent an overutilization of chemotherapy as the survival advantage and the QoL improvement induced by chemotherapy were unknown before 2003. The utilization rates in Canada (61% during 2003–2005) and Australia (54% during 2007–2009) seemed to be reasonably comparable to the estimated optimal chemotherapy utilization rate,^{8,10} while in countries such as the UK (18% between 2002 and 2005) and the Netherlands (36% between 2005 and 2006), the rate appeared to be significantly lower.^{9,13} The reasons for apparent underutilization in these two countries is unclear. It is likely that availability of chemotherapy drugs and regulatory issues shortly after the registration of pemetrexed may have impacted on the chemotherapy utilization rate.

It is important to consider the definition of the optimal chemotherapy utilization rate as it can affect the interpretation of the results. As stated, it is defined as an evidence-based estimation of the proportion of patients with MPM with an indication for chemotherapy based on evidence-based guideline recommendations. Therefore, “real world” situations have not been taken into account in the proposed model, such as an overrepresentation of elderly MPM patients. The median age of patients treated in the Vogelzang study was around 60 years,³ which is considerably lower than that of MPM patients in population-based studies (over 70 years of age).^{9,10} It is conceivable that the presence of the geriatric syndrome of frailty increases with age and by virtue of frailty, a proportion of elderly would not be deemed appropriate for chemotherapy treatment. However, frailty is likely to be accounted for by poor performance status, which is accounted for in the current analysis.

While the presence of severe comorbidities was not explicitly stated as an exclusion criterion in the pivotal studies,^{3,4} it is highly likely that investigators would avoid enrolling patients with major comorbidities (such as symptomatic heart failure) and performance status of ECOG 2 into the clinical trial. This is the rationale for including the presence of severe comorbidities in the sensitivity analysis to account for this. Furthermore, it is not inconceivable that patients with a performance status of ECOG 2 may not derive any benefits from combination chemotherapy, as there appears to be some conflicting data in non-small-cell lung cancer.^{30,31} This issue has not yet been examined in MPM, and,

consequently, we were unable to incorporate this in our utilization model.

It is our intention to further explore potential modifiable barriers for treatment and to verify if a population-based survival advantage could be realized if those barriers were bridged. To that end, we hypothesize that chemotherapy utilization in MPM may be affected by a number of barriers. One of the barriers may be related to therapeutic nihilism; with clinicians not recommending chemotherapy as they perceive that the improvement in median overall survival of 2–3 months outweighs potential side effects. This may lead clinicians to assume that patients will not consider chemotherapy to be worthwhile. At an individual level, chemotherapy is considered worthwhile if the likely benefits outweigh likely harms. This trade-off is known as a patient's "preference" for chemotherapy and is a personal judgment that differs from one individual to another. Although there are no studies of patients' preferences for chemotherapy in MPM, studies in patients with non-small-cell lung cancer demonstrated that individual patient preferences varied widely: from very small (where they would undergo chemotherapy for an expected survival benefit of 1%) to very large (where they would require a survival benefit of 50% to undergo chemotherapy).³² This highlights the importance of asking individual patient's their views about chemotherapy rather than making judgments on their behalf. Interestingly, in the UK study by Chapman *et al.*,⁹ 52% of patients eligible for, and who were offered, chemotherapy declined treatment. While this may represent patient preferences, it may simply reflect therapeutic nihilism.

There is also evidence that some MPM patients and their carers felt that the care provided was suboptimal,^{33,34} with fragmented care pathways and poorly coordinated care during the time of their illness which negatively impacted treatment decisions.

Geographical factors may also limit chemotherapy being utilized due to reduced access for patients from more remote locations. In support of this concept, an Australian qualitative study documented that some MPM patients in regional Australia felt that substantial side effects, potential costs associated with traveling for treatment and outpatient visits and the potential need for admission to a metropolitan hospital were factors that impacted on their and their carer's decision making.^{33,34}

The potential discrepancy between actual and optimal chemotherapy utilization rates provides a rationale to explore clinicians' and patients' attitudes to chemo-

therapy for MPM, including potential barriers and patient preferences. We are currently undertaking a quantitative and qualitative study to examine this issue in MPM patients, their carers and health professionals. We are also involved in a population-based study using central registry data to examine the pattern of chemotherapy utilization in New South Wales, Australia, before and after pemetrexed became reimbursed in Australia.

There are a number of potential limitations in this study. The characteristics of MPM patients at the time of diagnosis are not well documented in the literature, with no large epidemiological datasets reporting the performance status of MPM patients. The only available information we found was in a UK study by Chapman *et al.*,⁹ which reported 65% of patients having an ECOG performance status of 0–2. However, the chemotherapy utilization rate in this study was significantly lower than other high-income countries (i.e. 18% *vs* 61% in Canada),^{7,8,10,13} which may indicate that the study population is not representative of MPM patients seen in other countries. Therefore, the estimate that 65% of patients have good performance status may be an underestimation. There are no Australian data that document performance status in MPM patients, but in a similar disease population of stage IV non-small-cell lung cancer patients in New South Wales, 79% had a ECOG performance status of 0–2.²³ As stated before, patients' age was not addressed in the model, as it is generally closely related to performance status and was not an exclusion criterion for the clinical trials. The issue of patient comorbidities is complex. In the same UK study,⁹ it was documented that the proportion of patients with severe comorbidities was 24%. However, current practice guidelines do not provide specific information regarding how comorbidities affect the suitability of patients for chemotherapy, but rather use performance status as a surrogate and an indicator of overall fitness for chemotherapy. Certainly, severe comorbidities were not explicit exclusion criteria for entering the two reported phase III chemotherapy trials.^{3,4} We included comorbidities in the sensitivity analysis as we believe that the presence of significant comorbidities may influence whether or not chemotherapy is recommended. As discussed previously, there is no literature on patient preferences for chemotherapy in MPM and therefore the potential effect of this on the optimal utilization rate could not be determined. Taking all these together, we believe that our estimated optimal utilization rate is quite conservative.

CONCLUSION

In conclusion, our evidence-based model reveals that 65% of MPM patients should have chemotherapy at least once during the course of their illness. While this rate is relatively comparable to the actual chemotherapy utilization rates in some countries such as Canada and Australia, it appears lower in others such as the UK and the Netherlands. Although the current model is restricted by the limited data available in the MPM literature and therefore the seemingly underused rate of chemotherapy may be explained by historical reasons such as availability of pemetrexed and regulatory issues or attributes not accounted for in the model such as older age, the potential underutilization in some population may be modifiable. If this is the case, this presents an important impetus to better understand the potential barriers in the uptake of chemotherapy for patients with this devastating disease in order to develop strategies to overcome the barriers and improve patient outcomes.

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