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Effects of tumor burden reduction on survival in epithelioid malignant pleural mesothelioma

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Abstract

Objective: To understand the relationship between response and survival in malignant pleural mesothelioma (MPM) we assessed the outcomes of patients treated in the randomized clinical trial of cisplatin and pemetrexed versus cisplatin which resulted in the only United States Food and Drug Administration approved regimen for MPM.

Methods: The original clinical trial was conducted from April 1999 to March 2001. Patients with epithelioid MPM (n = 305) were categorized using modified pleural Response Evaluation Criteria for Solid Tumors (mRECIST) by whether or not they responded to treatment. Median progression-free survival (PFS) and overall survival (OS) were estimated and the hazard ratios for responders and non-responders were estimated and compared by the log rank test. Multivariable Cox proportional hazards models were used to adjust for baseline prognostic factors.

Results: Patients who responded to front-line therapy had a significantly longer OS (HR 0.34, 95% CI 0.24–0.49; median 20.6 months, 95% CI: 15.3–not reached) than those who did not respond (median 9.4 months, 95% CI: 8.1–11.0; P<.001). Similarly responders had a significantly longer PFS (HR 0.50, 95% CI: 0.39–0.64; median 7.8 months, 95% CI: 6.5–8.5) compared to non-responders (median 3.7 months, 95% CI: 2.9–4.3; P<.001). These results were confirmed when

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Conflict of Interest Statement:

Dr. Mansfield reports payments to his institution from AbbVie, Genentech, BMS and Trovogene for consulting, and payment to his institution from Novartis for research. All other authors have no relevant conflicts of interest.

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adjusting for baseline prognostic factors. We also observed a survival benefit associated with disease stabilization in MPM.

Conclusions: In summary, our findings demonstrate that a reduction in tumor burden or disease stabilization determined by mRECIST is strongly associated with OS and PFS in epithelioid MPM.

Introduction

While commonly used, surrogate endpoints remain controversial in anticancer drug approvals despite their acceptance by regulatory agencies¹. In fact, one review of oncology drug approvals from 1990–2002 showed that 68% of approvals were based on endpoints other than survival². Pharmaceutical industry support of and increasing public demand for accelerated access to novel therapies further encourages the use of surrogate endpoints³; however, these endpoints must provide reliable and robust surrogates for patient outcomes. Objective Response rate (ORR) is commonly used as an endpoint in early phase clinical trials and is increasingly incorporated in phase 3 clinical trials, but due to limited duration of response, drug toxicity or due to other factors a response to treatment may not necessarily translate into improved survival.

Despite the dismal prognosis of malignant pleural mesothelioma (MPM), targeted therapies⁴, auxotrophic strategies⁵ and immunotherapy^{6,7} demonstrate emerging signals of improved patient outcomes. These pharmaceutical developments have led to a proliferation of clinical trial opportunities for patients with MPM, many of which incorporate ORR into their trial design. To date, as the effect of tumor burden reduction on survival in MPM remain indeterminate the widespread use of ORR as a study outcome mandates clinical validation.

Assessment of disease progression remains challenging in MPM and standard Response Evaluation Criteria for Solid Tumors (RECIST)⁸ were not designed to measure pleural disease. Modified pleural RECIST (mRECIST)⁹ have been adopted by mesothelioma experts for measuring disease response in clinical practice and in clinical trials for MPM.

Combination therapy with cisplatin and pemetrexed represents the only United States Food and Drug Administration (FDA) approved regimen for MPM. In the clinical trial that led to the approval of this regimen, patients were randomized to receive either cisplatin or cisplatin and pemetrexed. The median survival for patients who received the doublet was 12.1 months compared to 9.3 months for those who received cisplatin alone¹⁰. The effects of treatment response on survival have not been reported for this clinical trial. Herein we report the relationship of treatment response based on mRECIST to progression-free survival (PFS) and overall survival (OS) in patients with epithelioid MPM treated with the only FDA-approved regimen for this disease.

Methods

We requested and received approval from the sponsor (Eli Lilly and Company) to use the data collected from the clinical trial that led to approval of cisplatin and pemetrexed by the

FDA for MPM¹⁰ through clinicalstudydatarequest.com. The original clinical trial was conducted from April 1999 to March 2001. Since the majority of patients had epithelioid MPM and disease responses were rare among patients with sarcomatoid MPM, we limited our analysis to the subset of patients with epithelioid mesothelioma. Additionally, patients were also administered folic acid and vitamin B12 to reduce the toxicity of pemetrexed part way through this clinical trial. Accordingly, we assessed outcomes amongst all cases of epithelioid MPM, and amongst those who received supplementation. Responses were categorized using mRECIST⁹ as determined by treating investigators. Response assessment was performed per protocol which was at least once just before every other treatment while a patient was receiving study therapy and approximately every 6 weeks after completion of study therapy. Treatments were scheduled every 21 days. Progression-free survival (PFS) and overall survival (OS) were analyzed to assess differences between responders and non-responders. Kaplan Meier techniques were used to estimate survival rates. Cox proportional hazards models were used to estimate the magnitude of risk of death/progression of responders compared to non-responders, or responders and those with stable disease compared to those with progression. To assess the robustness of these results, multivariable Cox proportional hazards models were used including previously reported baseline prognostic factors (performance status, stage, age, white blood cell count, hemoglobin concentration, platelet count, and patient reported pain)^{11,12}. Mayo Clinic's Institutional Review Board approved this study.

Results

We analyzed 305 patients with epithelioid MPM. There were 98 patients (32%) with a complete response (CR) or partial response (PR), 126 patients (41%) with stable disease (SD) as their best response and 81 patients (27%) with progression of disease (PD). We identified that patients who responded (CR and PR) to front-line therapy with cisplatin or cisplatin and pemetrexed had a significantly longer OS (HR 0.34, 95% CI 0.24–0.49; median 20.6 months, 95% CI: 15.3–not reached) than patients who did not respond (SD or PD) to treatment (median 9.4 months, 95% CI: 8.1–11.0; $P<.001$; **Figure 1A**). Similarly, patients who responded to front-line therapy had a significantly longer PFS (HR 0.50, 95% CI: 0.39–0.64; median 7.8 months, 95% CI: 6.5–8.5) than those who did not respond (median 3.7 months, 95% CI: 2.9–4.3; $P<.001$; **Figure 1B**). These results were confirmed with multivariable modeling including baseline prognostic factors. The adjusted OS response group hazard ratio was 0.29 (95% CI: 0.20–0.41). Similarly, results for PFS were confirmed as the adjusted PFS response group hazard was 0.45 (95% CI: 0.35–0.59).

Our analysis of the effects of treatment response on survival restricted to patients who received supplementation with folic acid and vitamin B12 ($n=229$), included 80 patients (35%) with a CR or PR, 93 patients (41%) with SD as their best response, and 56 patients (24%) with PD. We observed that supplemented patients with epithelioid MPM who responded to front-line therapy had a significantly longer OS (HR 0.36, 95% CI 0.23–0.55; median 18.4 months, 95% CI: 14.9–not reached.) than patients who did not respond to treatment (median 10.8 months, 95% CI: 8.3–12.7 months; $P<.001$; **Figure 1C**). Similarly, supplemented patients who responded to front-line therapy had significantly longer PFS (HR 0.57, 95% CI 0.42–0.75; median 7.8 months, 95% CI 6.1–8.5 months) than patients who did

not respond to treatment (median 3.9 months, 95% CI 2.9–4.4 months; $P<.001$; **Figure 1D**). Again, these results were confirmed with multivariable modeling including baseline prognostic factors. The adjusted OS response group hazard ratio was 0.29 (95% CI: 0.19–0.45). Similarly, results for PFS were confirmed as the adjusted PFS response group hazard ratio was 0.50 (95% CI: 0.37–0.67).

To determine the effects of response to treatment or disease stabilization on survival we then grouped patients with CR, PR and SD as their best response ($n=224$), and we compared them to patients with PD ($n=81$). We first assessed all patients with epithelioid MPM. We observed that patients with response to treatment or disease stabilization had a significantly longer OS (HR 0.24, 95% CI 0.17–0.33; median 14.9 months, 95% CI 12.8–17.2 months) than patients with PD (median 5.7 months, 95% CI 4.0–6.5 months; $P<.001$; **Figure 2A**). Similarly, the PFS of patients with response to treatment or disease stabilization was significantly longer (HR 0.18, 95% CI 0.14–0.24; median 6.3 months, 95% CI 5.8–7.0 months) than patients with PD (median 1.4 months, CI not determined; $P<.001$; **Figure 2B**). These results were confirmed with multivariable modeling including baseline prognostic factors. The adjusted hazard ratio for OS was 0.22 (95% CI 0.16–0.31) and for PFS was 0.19 (0.14–0.25).

When then restricted our analysis to patients who received supplementation with folic acid and vitamin B12. We observed that supplemented patients with response to treatment or disease stabilization had a significantly longer OS (HR 0.25, 95% CI 0.18–0.37; median 15.4 months, 95% CI 13.3–17.6 months) than patients with PD (median 5.9 months, 95% CI 4.4–6.7 months; $P<.001$; **Figure 2C**). Similarly, the PFS of patients with response to treatment or disease stabilization was significantly longer (HR 0.22, 95% CI 0.16–0.31; median 6.3 months, 95% CI 5.8–7.3 months) than patients with PD (median 1.4 months, 95% CI 1.4–1.5 months; $P<.001$; **Figure 2D**). These results were confirmed with multivariable modeling including baseline prognostic factors. The adjusted hazard ratio for OS was 0.23 (95% CI 0.15–0.34) and for PFS was 0.20 (0.14–0.29).

Finally, we separately assessed the survival of patients with CR/PR, SD and PD. Amongst all patients, and the supplemented patients, we observed that OS and PFS were best amongst patients with CR/PR. For patients with SD as their best response to treatment, the OS and PFS outcomes were between those of responders and those with PD (**Figure 3; Table 1**).

Discussion

We observed that treatment response to single agent cisplatin or the combination cisplatin and pemetrexed in patients with epithelioid MPM as defined by mRECIST is strongly associated with OS and PFS. These findings are supportive of the use of ORR as an endpoint in clinical trials for MPM, but there are caveats to the indiscriminate acceptance such use. Novel therapeutic approaches, especially immunotherapies, challenge our traditional response assessments, and a radiographic increase in the size of a lesion may actually represent infiltration of tumor by lymphocytes rather than disease progression¹³. In the clinic, it can be challenging to distinguish cases of disease progression from pseudo-progression with immunotherapy. Additionally, targeted therapies may result in dramatic

reductions of tumor burden, but these responses may be short lived and may not always correlate with survival benefits. We also observed that stabilization of disease was associated with a survival benefit. Along these lines, endpoints such as PFS may be more appropriate than response rates for investigational or therapeutic agents that stabilize tumors rather than shrink them.

The original proposal for mRECIST evaluated how response to cisplatin and gemcitabine affected survival in 73 patients with MPM, and identified a significant correlation between treatment responses and improved overall survival⁹. Since the FDA approved the frontline regimen of cisplatin and pemetrexed for MPM, the cisplatin and gemcitabine regimen is less commonly used. Regardless, our results support this observation. It is important to note that we used the mRECIST-based responses as determined by the treating investigators. Secondary review of the data by the FDA did not confirm all of these responses¹⁴, however it remains unclear whether the FDA used mRECIST or RECIST in their assessment of treatment responses which may explain this discrepancy. Others have studied surrogate endpoints in mesothelioma. One recent retrospective review of patient outcomes from 17 phase 2 clinical trials conducted by CALGB or NCCTG (now the Alliance) did not identify a strong association between PFS and OS¹⁵. There were very few responses in the clinical trials in this analysis, and the association between treatment response and survival was not addressed, which limits comparison with our study. In the study most similar to ours, patients who were treated on phase 2 clinical trials conducted by the European Organization for Research and Treatment of Cancer (EORTC) were assessed for response at a 42-day landmark. Overall survival was significantly different between those who achieved a partial response (12.8 months), stable disease (9.4 months) or progressive disease (3.4 months)¹⁶. A separate study based on many of the same patients assessed PFS rates at 9 and 18 weeks and found that both were predictive of overall survival¹⁷. In order to limit selection bias landmark analysis, removing patients who died or were censored prior the landmark, was used in these studies. Consequently control arms are less penalized for early deaths; however a significant proportion of patients, 16.8% and 27.9%, respectively removed for the PFS rate analysis at 9 and 18 weeks¹⁷. We argue that while a landmark analysis with a more distant time point would assess the impact of the durability of response on survival, too distant of an endpoint may not provide a meaningful comparison. In order to minimize such bias in our study, we used multivariable Cox proportional hazards models to adjust for known prognostic factors in mesothelioma. Regardless of these differences in approaches, similar conclusions can be made for our studies that responses to treatment are associated with an overall survival benefit in MPM. Despite our observations we acknowledge that mRECIST remain suboptimal for a spatially complex disease such as MPM. More comprehensive linear measurements and possibly serial volumetric assessments of tumor size using CT, MRI or PET-CT represent future opportunities for improvement^{18–21}.

More recently, the addition of bevacizumab to cisplatin and pemetrexed improved OS and PFS compared to cisplatin and pemetrexed alone²². It is not certain if the addition of an anti-vascular endothelial growth factor agent affects the association of response and survival, as it was not reported in that study. Even though the addition of bevacizumab to cisplatin and gemcitabine did not improve PFS or OS in patients with MPM²³, its inclusion with cisplatin and pemetrexed is associated with a strong incremental benefit in patient survival.

The gold standard outcomes for oncology clinical trials are overall survival and quality of life, but cross over to subsequent therapies and competing risks influence measurement of survival. Our results are confounded by second-line therapies which were administered to 42% (189/448) of the patients who participated in the front-line clinical trial²⁴. Those who received second-line therapy had significantly improved survival compared to those who did not. Due to the limited numbers and low treatment response rates we excluded patients with sarcomatoid MPM in this trial from our analysis; however, we have published on the response rates of these patients previously²⁵. Consequently, our current findings should not be extended to other subtypes of MPM. Additionally, we are uncertain how our findings apply to subsequent lines of therapy, other chemotherapeutic regimens, targeted agents or immunotherapy. Some investigators argue that there is no standard of care second line therapy for MPM, and that clinical trial participation, in clinical trials that stratify based on prognostic scores, is desirable²⁶. We share that opinion. Regardless, the strong association we observed of ORR with survival supports the inclusion of ORR in early phase clinical trials or as secondary endpoints in phase 3 trials. The decision to include ORR as an endpoint should be based on the nature of the therapeutic agent being studied, guidance from the FDA or other relevant regulatory agencies, and the methods and frequency of response assessment.

Conclusions

In summary, our findings demonstrate that a reduction in tumor burden or disease stabilization determined by mRECIST is strongly associated with OS and PFS in epithelioid MPM.

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Abbreviations

CI	confidence interval
FDA	United States Food and Drug Administration
MPM	malignant pleural mesothelioma
mRECIST	modified pleural Response Evaluation Criteria in Solid Tumors
ORR	objective response rate
OS	overall survival
PFS	progression free survival
RECIST	Response Evaluation Criteria in Solid Tumors
CR	complete response

PR	partial response
SD	stable disease
PD	progression of disease

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Figure 1:

Survival outcomes of responders (CR/PR) compared to others (SD/PD). The KM plots of OS (A) and PFS (B) are shown for all patients and for the patients who received supplementation (C and D for OS and PFS respectively).

Figure 2:
Survival outcomes of clinical benefit group (CR/PR/SD) compared to others (PD). The KM plots of OS (A) and PFS (B) are shown for all patients and for the patients who received supplementation (C and D for OS and PFS respectively).

Figure 3:

Survival outcomes of all groups separately (CR/PR v SD v PD) The KM plots of OS (A) and PFS (B) are shown for all patients and for the patients who received supplementation (C and D for OS and PFS respectively).

Table 1:

Sample sizes and survival outcomes by groups

Median Overall and Progression-Free Survival Times (Months)				
	Overall Survival		Progression-Free Survival	
Group	Median	CI	Median	CI
Epithelial Population (N=305)				
CR/PR	20.6	15.3, NA	7.8	6.5, 8.5
SD	12.2	10.8, 14.8	5.5	4.5, 6.2
PD	5.7	4.0, 6.5	1.4	NA
CR/PR/SD	14.9	12.8, 17.2	6.3	5.8, 7.0
SD/PD	9.4	8.1, 11.0	3.7	2.9, 4.3
Epithelial and Supplemented Population (N=229)				
CR/PR	18.4	14.9, NA	7.8	6.1, 8.5
SD	13.3	11.4, 16.0	5.5	4.5, 6.5
PD	5.9	4.4, 6.7	1.4	1.4, 1.5
CR/PR/SD	15.4	13.3, 17.6	6.3	5.8, 7.3
SD/PD	10.8	8.3, 12.7	3.9	2.9, 4.4

CR = complete response, PR = partial response, SD = stable disease, PD = progression of disease, CI = confidence interval