Published in final edited form as:

Lung Cancer. 2014 November ; 86(2): 133–136. doi:10.1016/j.lungcan.2014.08.017.

Systematic review of response rates of sarcomatoid malignant pleural mesotheliomas in clinical trials

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Abstract

Rationale—Malignant pleural mesothelioma is an almost universally fatal malignancy primarily related to asbestos exposure. Based on the differences in immunologic markers and gene expression between histologic subtypes of mesothelioma, and our clinical impression that response rates vary by histology, we decided to examine the reported response rates of mesothelioma subtypes.

Objectives—Our objective was to compare the response rates of sarcomatoid mesotheliomas to the overall response rates in published clinical trials.

Methods—We searched PubMed for “mesothelioma” with the clinical trials filter selected. We included articles published between January 1, 2000 and March 20, 2014 in which subjects received first or second line systemic therapy for malignant pleural mesothelioma. Studies investigating multi-modality therapy including surgery were excluded. Response rates [including 95% confidence intervals (95% CI)] were estimated for the entire patient cohort and then separately for subjects with sarcomatoid tumors.

Measurements and Main Results—We reviewed 544 publications of which 41 trials met our inclusion criteria. Eleven of these trials did not include patients with sarcomatoid mesothelioma (27% of eligible studies). The remaining 30 publications included 1475 subjects, 1011 with epithelioid tumors (68.5%), 203 with biphasic tumors (13.8%), 137 with sarcomatoid tumors (9.3%) and 124 with unknown subtypes (8.4%). In total, there were 323 responses (21.9%, complete and partial responses, 95% CI: 16.3, 28.8) to systemic therapy across all histological

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All authors contributed to the design, data acquisition, analysis, and drafting of this work. All authors provide final approval and are accountable for all aspects of the work.

Disclaimers: None

subtypes. In patients with sarcomatoid tumors (n=137) 19 responses were observed. This accounted for 5.9% of all responses and yields a 13.9% (95% CI: 8.6, 21.6) response rate for patients with sarcomatoid tumors. Multiple biases likely affected this systematic review.

Conclusion—Response rates for different histological subtypes of malignant pleural mesothelioma are infrequently reported. Partial and complete responses to systemic therapies appear to be less common among patients with sarcomatoid tumors.

Keywords

mesothelioma; epithelioid; sarcomatoid; systematic review; response rates

[1.0] Introduction

[1.1] Malignant pleural mesothelioma (MPM) represents an almost universally fatal disease most frequently attributed to prior asbestos exposure. There are limited treatment options and there remains significant controversy regarding the role of surgery for MPM [1, 2]. Although asbestos exposure has been significantly reduced in North America and Europe, due to the delayed onset of the disease the projected peak incidence of MPM has yet to occur in some Western countries whereas it has plateaued in others including the United States [3]. Furthermore, globally the incidence of MPM is expected to continue to increase considering ongoing asbestos mining [4, 5] and continued exposure to asbestos in heavily-populated countries like India and China [6].

[1.2] Although current guidelines do not differentiate the treatment recommendations of advanced stages between histological subtypes of MPM, sarcomatoid tumors very rarely benefit from aggressive multi-modality therapy including surgical resection. Anecdotally these observations are also extended to medical therapies and patients with non-epithelioid histology are excluded from some clinical studies. Recent data suggest that there are potentially important genetic and immunologic differences between the histological subtypes of MPM. We recently reported significant differences in the expression of immune checkpoint molecules among different mesothelioma subtypes. Specifically, sarcomatoid mesotheliomas almost universally expressed programmed cell death 1 ligand 1 (PD-L1), whereas it was only expressed by 16% of the epithelioid tumors [7]. Furthermore, some genetic abnormalities, such as inactivation of the BRCA1 associated protein-1 (*BAP1*) tumor suppressor gene vary based on the histological subtype. BAP-1 mutation appears to be more common among epithelioid tumors [8].

[1.3] In light of these genetic and immunological differences and the clinical perception that sarcomatoid tumors are less responsive to treatment including systemic therapies we decided to examine the reported response rates for patients with sarcomatoid MPM in the literature.

[2.0] Methods

[2.1] On March 10, 2014 PubMed (www.ncbi.nlm.nih.gov/pubmed) was searched for clinical trial using the search term “mesothelioma”. We included all articles published between January 1, 2000 and March 20, 2014. This timeline was chosen to ensure unified

diagnostic criteria for MPM. The aggregate and histological subtype specific response rates, specifically focused on subjects with sarcomatoid mesotheliomas, who received either systemic first or second line therapies for MPM were abstracted by one author (ASM) into a data extraction form. Too few studies included information on survival by subtype for abstraction. Only response rates were combined for our analysis. In addition the authors of the treatment-defining study of cisplatin and pemetrexed were specifically contacted and additional data regarding subtype specific responses rates were obtained for this analysis. The authors did not conduct a risk of bias as most of the included studies were not randomized. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses was reviewed and utilized for the study [9]. PowerPoint (Microsoft Office Standard 2010, Microsoft Corporation Redmond, WA) and Photoshop (Adobe Systems Incorporated San Jose, CA) were used for figure creation. Response rates [including 95% confidence intervals (95% CI)] were estimated for the entire patient cohort and then separately for subjects enrolled to trials designed for only first-line therapy and subjects enrolled to the complementary trials. For each cohort, a logistic regression model was used that included an intercept as a fixed factor and an over-dispersion parameter to account for trial variability using SAS version 9.3 (Cary, North Carolina).

[3.0] Results

[3.1] There were 544 publications, 153 of them were published within our timeline and the titles or abstracts suggested that a systemically administered agent was studied in patients with MPM. One hundred twelve articles were excluded because: the studies included tumor types other than MPM and the MPM histological subtypes were not identified (n=23), the results were not reported by subtype or could not be deduced (n=29), a retrospective review was reported (n=2), a post-trial analysis of outcomes other than response was reported (n=7), a preclinical study was reported (n=1), maintenance therapy after response to induction therapy was reported (n=1), results of an expanded access protocol were reported (n=4), multimodality therapy for resectable candidates was reported (n=19), no systemic therapy was administered or intracavitary treatment was delivered (n=14), the study only reported subjects with peritoneal mesothelioma (n=1), the subtypes were not reported in the patient characteristics (n=10), and the manuscript was not in English or not available for review (n=1).

[3.2] Of the remaining 41 clinical trials, 11 did not include any patients with sarcomatoid mesothelioma, even though there was no mention that this histological subtype was excluded in the methodology (Figure 1). Accordingly, 30 clinical trials (Table 1) reported the response rate by histological subtype, was obtained by the study authors, or allowed the determination of the response rate for sarcomatoid tumors to be deduced if all the responders had epithelioid tumors. In these 30 trials there was a total of 1475 subjects, including 1011 subjects with epithelioid tumors (68.5%), 203 with biphasic tumors (13.8%), 137 with sarcomatoid tumors (9.3%) and 124 with unknown subtypes (8.4%). In total, there were 323 complete or partial responses or an overall response rate of 21.9% (95% CI: 16.3, 28.8). There were 19 responses in patients with sarcomatoid tumors accounting for 5.9% of all responses and a response rate of 13.9% (95% CI: 8.6, 21.6). Eighteen of these responses were observed in subjects treated with first-line therapy, resulting in a first-line response rate

of 16.7% (95% CI: 9.7, 27.2). The response rate in the complementary group of trials was 3.5% (95% CI: 0.5, 20.8).

[4.0] Discussion

[4.1] Our review demonstrates that response rates based on the histological subtype of MPM are reported in a minority of publications. Based on the available data, subjects with sarcomatoid mesotheliomas appear to have fewer complete or partial responses compared to subjects with other subtypes. Given the genetic and immunologic differences between mesothelioma subtypes, future clinical trials investigating new targeted agents may benefit from subtype specific analysis. Additionally, although sarcomatoid tumors were not specifically excluded based on the reported eligibility criteria, our findings suggest that none of these subjects were included in 27% of mesothelioma-specific clinical trials. While this could reflect the small sample size of these studies and the lower prevalence of sarcomatoid tumors, it could also be attributable to investigator bias towards enrolling patients with better treatment responses (epithelioid tumors). Furthermore it is possible that the inclusion criteria were incompletely reported in the manuscripts. The incidence of sarcomatoid tumors (9.3%) in our final analysis of 30 clinical trials is within range of the reported incidence in a French surveillance study (11%)[10], and that of the International Association for the Study of Lung Cancer Mesothelioma Database (8.2%)[11].

[4.2] We observed an aggregate response rate of 21.9% for all patients, and 13.9% for patients with sarcomatoid tumors. Almost all of the responses in these tumors occurred with first line therapy and potentially successful systemic therapeutic agents included cisplatin, carboplatin, gemcitabine and vinorelbine. Overall, these findings suggest that consideration should be given to experimental therapeutics in the way of clinical trials for patients with sarcomatoid mesothelioma given their poor prognosis and lower likelihood to receive or respond to second line therapy. In a post hoc analysis of the phase III clinical trial that defined the current frontline systemic regimen for mesothelioma, an overall response rate of 41.3% (95% CI: 34.8, 48.1) was observed in the 225 subjects with measureable disease at baseline and who received cisplatin and pemetrexed [12]. In comparison, there was an overall response rate of 22.2% (95% CI: 6.4, 47.6) among 18 subjects with sarcomatoid tumors. There were two other trials included in this review that tested pemetrexed-based regimens; however, these trials utilized carboplatin instead of cisplatin [17, 18]. These two trials included in total twelve subjects with sarcomatoid mesothelioma and none of them responded to treatment. In other words, four out of 30 (13%) subjects treated with pemetrexed-based regimens responded to treatment in comparison to the 15 responders of 107 (14%) subjects treated with non-pemetrexed-based regimens. Given the variety of non-pemetrexed-based regimens tested and the overall paucity of responses, it is challenging to conclude whether another regimen is equivalent or superior to the current standard of care. Regardless, these data reflect the desperate need for improved therapies for mesothelioma, particularly sarcomatoid mesothelioma.

[4.3] There were several limitations to this systematic review. Most importantly, only a minority of trials reported responses by subtype. Additionally, 8.4% of the subjects in our analysis had unknown subtypes and their response rates were almost never reported

separately. We were unable to abstract data on demographics, stable disease, progression-free survival and overall survival by subtype in all but a few publications. This review is certainly subject to biases that affect the trials themselves. Specifically, due to sampling error some patients might be diagnosed as having an epithelioid or sarcomatoid subtype instead of biphasic disease. Moreover, there was no central review of histologic subtypes in the reported studies. Additionally, the measurement of response in mesothelioma is challenging and we were not able to confirm the reported responses. Furthermore, with the introduction of the modified response evaluation criteria in solid tumors for MPM during our study period, the trials we reviewed utilized different measurements of response [13]. Although we suspect that there is a degree of publication bias and that some trials without activity have not been published, many of the studies we included reported negative findings. Despite these shortcomings, we were able to show that in the trials that reported responses by subtype, patients with sarcomatoid tumors had a lower response rate than seen on average in MPM even with the most widely adopted front line therapy.

[5.0] Conclusion

[5.1] The response rates of mesothelioma subtypes are reported in a minority of publications. Fewer responses are seen in subjects with sarcomatoid tumors and individualized therapy based on histological subtype should be considered for future clinical trials in MPM. Multiple biases including the participation of this subtype in clinical trials, sampling error, and reporting of responses likely affected this systematic review.

Acknowledgments

The authors would like to acknowledge Bobbi Jebens for her administrative support.

Support: NIH K23 CA159391 (TP)

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Highlights

- We compared overall response rates by subtypes in mesothelioma
- In a systematic review of 30 trials, 21.9% of patients responded to therapy
- In comparison, only 13.9% of patients with sarcomatoid subtypes responded
- Responses rates by subtypes of mesothelioma are infrequently reported
- Post-hoc analysis of cisplatin-pemetrexed trial by subtype included

Figure 1.
Flow diagram of systematic review

Table 1

The agents tested of the trials that reported responses by subtype are shown in addition to the line of therapy that was administered and the responses observed amongst the sarcomatoid cases

Agent(s)	Line of therapy	Sarcomatoid Responses [Response detected (#sarcomatoid responders/total # of sarcomatoid cases)]
Ifosfamide, mesna, interferon- α 2a [14]	First	None (0/2)
Tremilimumab [15]	Subsequent	None (0/3)
Cediranib[16]	Multiple	None (0/2)
Carboplatin, pemetrexed [17]	First	None (0/7)
Carboplatin, pemetrexed, bevacizumab [18]	First	None (0/5)
Vinorelbine, oxaliplatin [19]	First	Yes (1/5)
Bortezomib [20]	Multiple	None (0/3)
Gefitinib [21]	First	None (0/3)
Carboplatin, liposomal doxorubicin, gemcitabine [22]	First	Yes (5/24)
Liposomal doxorubicin [23]	First	None (0/4)
Erlotinib, bevacizumab [24]	Subsequent	None (0/2)
Gemcitabine, cisplatin [25]	First	None (0/4)
Irinotecan [26]	First	None (0/6)
Gemcitabine [27]	First	None (0/5)
Docetaxel and irinotecan [28]	First	None (0/2)
Cisplatin and prolonged infusion of low dose gemcitabine [29]	First	Yes (1/4)
Imatinib [30]	Multiple	None (0/1)
Interleukin-2 [31]	First	None (0/1)
Cisplatin and gemcitabine [32]	First	Yes (3/7)
Sunitinib [33]	Second	None (0/1)
Liposomal doxorubicin [34]	Multiple	None (0/3)
Gemcitabine and epirubicin [35]	Multiple	Yes (1/10)
Cisplatin, doxorubicin, interferon- α 2b [36]	First	Yes (2/4)
Mitoxantrone, methotrexate, mitomycin [37]	First	None (0/1)
Ralitrexed, oxaliplatin [38]	Second	None (0/3)
Belinostat [39]	Second	None (0/1)
Pegylated, liposomal doxorubicin [40]	First	None (0/1)
Vinorelbine [41]	First	Yes (2/2)
Ifosfamide, mesna, granulocyte-colony stimulating factor [42]	First	None (0/3)
Cisplatin, pemetrexed [12]	First	Yes (4/18)