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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 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.

1. Introduction

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].

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

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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].

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. Methods

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 from. 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 Systematics Reviews and Mata-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, NC).

3. Results

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 ($n = 1$).

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 (Fig. 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 for 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).

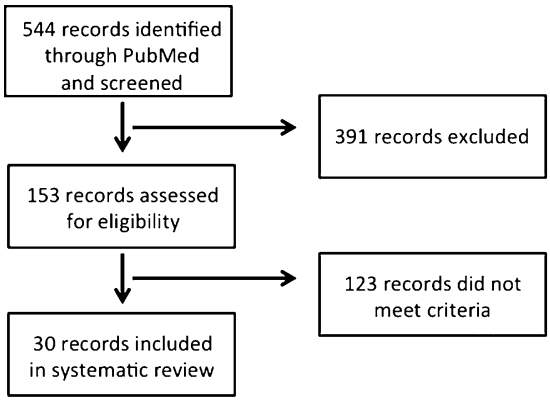

Fig. 1. Flow diagram of systematic review.

4. Discussion

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 toward 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].

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 first-line experimental therapeutics in the way of clinical trials for patients