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Short communication

Pathological complete response in malignant pleural mesothelioma patients following induction chemotherapy: Predictive factors and outcomes

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ABSTRACT

A small proportion of patients with malignant pleural mesothelioma (MPM) achieve pathological complete response (CR) following treatment with current practice induction chemotherapy. Our analysis of 58 patients with MPM treated with platinum-based chemotherapy showed 4 patients (7%) attained pathological CR at subsequent extrapleural pneumonectomy (EPP). Patient and tumour factors such as age, gender, smoking habit, histological subtype, and clinical stage were not found to be associated with pathological CR. Patients with pathological CR had longer disease-free survival (29.2 vs. 13.8 months; p = 0.08) and overall survival (76.4 vs. 23.4 months; p = 0.06) but this did not reach statistical significance. Our study suggests that patients who achieve pathological CR after chemotherapy may have improved survival in MPM.

1. Introduction

Malignant pleural mesothelioma (MPM) is an uncommon asbestos-related cancer arising from the mesothelial cell lining of the lung. This highly aggressive tumour typically affects older males 30–40 years after initial asbestos exposure and generally carries a poor prognosis [1]. Current recommendations are that patients with good performance status should be treated with first-line combination chemotherapy of platinum and either pemetrexed or raltitrexed [2,3], with a radiological response rate of 41.3% in cisplatin/pemetrexed treated patients [4]. Addition of anti-angiogenic targeted therapies such as bevacizumab or nintedanib to standard chemotherapy has recently been shown to be a promising strategy [5,6]. A small proportion of patients with MPM may be eligible to proceed to radical surgery [7], but this approach remains controversial [8]. If radical surgery is adopted, it is generally agreed that it should be in the context of a multi-modal approach in combination with induction chemotherapy and/or radiotherapy. One such radical surgical approach is extrapleural pneumonectomy (EPP) involving the *en bloc* resection of pleura, lung, pericardium, and diaphragm, as well as systematic nodal dissection. This radical surgical procedure provides a unique opportunity to assess for pathological response to chemotherapy in MPM, which is rarely documented in the literature.

Hence, we aim to document the rate of pathological complete response (CR) to chemotherapy in MPM patients; to identify if there are any patient or tumour characteristics that are associated with this; and to determine if pathological CR is associated with favourable prognosis.

2. Methods

We retrospectively reviewed consecutive patients with a pathologically confirmed MPM who underwent induction che-

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Table 1
Patient demographics.

Patient characteristic		Frequency N = 58
Gender	Male	46 (79%)
	Female	12 (21%)
Age (years)	Median (range)	63 (32–90)
Smoking habit	Ever smokers	31 (53%)
	Never smokers	27 (47%)
Clinical stage	Stage I or II	30 (52%)
	Stage III	25 (43%)
	Missing	3 (5%)
Histological subtype	Epithelioid	52 (90%)
	Biphasic	6 (10%)
	Sarcomatous	0 (0%)
Types of chemotherapy	Cisplatin/pemetrexed	42 (72%)
	Carboplatin/pemetrexed	14 (24%)
	Carboplatin/vinorelbine	1 (2%)
	Carboplatin/paclitaxel	1 (2%)
Cycles of chemotherapy	Median (range)	3 (1–9)
Adjuvant radiotherapy	Yes	38 (66%)
	No	20 (34%)
Radiological response	Complete response (CR)	0 (0%)
	Partial response (PR)	38 (66%)
	Stable disease (SD)	18 (31%)
	Progressive disease (PD)	2 (3%)
Pathological response	Complete	4 (7%)
	Incomplete	54 (93%)

motherapy followed by EPP at two Sydney institutions (Royal Prince Alfred and Strathfield Private Hospitals) between January 2003 and July 2015. The study was approved by the local Human Research Ethics Committee (HREC) and a waiver of consent was granted given the retrospective nature of the study.

Pathological CR was defined as the absence of malignant cells on routine histological examination on complete resected surgical specimen. The prognostic factors examined in this study included histological subtype which was determined according to the World Health Organisation (WHO) guidelines (epithelioid versus non-epithelioid) [9]; the clinical stage which was assessed using both CT and PET imaging according to the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) guidelines (stage I–II versus stage III–IV) [10,11]; age (<65 versus ≥ 65 years); smoking status (ever smokers versus never smokers); gender; and radiological response to treatment according to the modified Response Evaluation Criteria In Solid Tumours (RECIST) criteria for mesothelioma (complete or partial response versus stable or progressive disease) [12].

The disease-free survival (DFS) was defined as the period from the date of EPP to date of radiological or pathological recurrence of malignancy, while overall survival (OS) was defined as the period from the date of EPP to date of death of any cause. Those who have not had an event were censored. The survival times were calculated by the Kaplan-Meier method, and comparison between those who achieved pathological CR versus those who did not was made using the log rank test. Factors associated with pathological CR were examined using the chi square test. Multivariate analyses were performed using the proportional hazards regression analysis (Cox) model, incorporating well known prognostic variables such as gender, histological subtype, and clinical stage. All statistical analyses were performed using IBM SPSS Statistics Version 22.

3. Results

A total of 58 patients were included in this study. Of these patients, four (7%) had a pathological CR when the surgically resected tissue was examined. Median DFS was 15.1 months (95% CI: 6.9–23.3 months) while median OS was 24.4 months (95% CI: 20.0–28.9 months). 43 deaths (74.1%) occurred during this study. Table 1 describes baseline patient and tumour characteristics.

None of the examined pretreatment patient- or tumour-related factors were significantly associated with pathological CR (Suppl Table 1). All four patients with pathological CR had MPM of the epithelioid histological subtype.

Median DFS was longer in patients with pathological CR: 29.2 months (95% CI: not reached) vs. 13.8 months (95% CI: 8.3–19.3 months) for those with and without pathological CR respectively; $p = 0.08$. Similarly, median OS was longer in patients with complete pathological response: 76.4 months (95% CI: 0–163.4 months) vs. 23.4 months (95% CI: 19.7–27.1 months); $p = 0.06$. (Fig. 1)

Cox regression analysis showed that absence of pathological CR was associated with worse DFS and OS. DFS hazard ratio (HR) was 4.51 (95% CI: 1.04–19.65) for patients without pathological CR compared to those with pathological CR; $p = 0.05$. Similarly, OS HR was 5.13 (95% CI: 1.17–22.57) between these two groups; $p = 0.03$. Female gender, epithelioid histological subtype and early clinical stage were not associated with improved DFS or OS in this analysis. Table 2 shows both univariate (Kaplan-Meier) and multivariate (Cox regression) analysis of these patient characteristics on survival.

4. Discussion

MPM was considered a treatment resistant tumour until the publication of the cisplatin/pemetrexed trial [4], where a 41.3% response rate was documented. Despite this moderate response rate, none of these patients achieved a radiological CR. In a phase II trial of carboplatin/pemetrexed, up to 4% of treated patients had radiological CR [13]. Documentation of pathological responses to chemotherapy has been rare, given that the majority of MPM patients are unsuitable for surgical resection. In some limited patient series in the literature [14–16], the rate of pathological CR was found to be 4% in two reports. This rare phenomenon was confirmed in our series where we documented a pathological CR rate of 7%. This is the first report to date where systematic evaluation was made in a retrospective series of patients with mature follow-up data to identify possible predictors of pathological CR and to assess if pathological CR has prognostic significance.

Given the heterogeneity of response in patients receiving chemotherapy for MPM, we set out to determine if patient and tumour related characteristics were associated with pathological CR. Age, gender, smoking habit, histological subtype, and clinical stage were not significantly associated with achievement of pathological CR. Interestingly, as in other reports, only patients with epithelioid histological subtype achieved pathological CR [14–16]. As in the series reported by Bech [15], some patients with more bulky tumour (stage III) also had pathological CR. In addition, one of the four patients who had pathological CR in our series had received carboplatin-based chemotherapy. This was also reported by the Bech series [15], suggesting that carboplatin may be used in MPM if cisplatin is contraindicated, potentially without compromising efficacy.

Furthermore, pathological CR in other solid organ tumours such as breast cancer is associated with longer DFS and OS [17] but this