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How does the timing of chemotherapy affect outcome following radical surgery for malignant pleural mesothelioma?

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ABSTRACT

Objectives: There is little evidence regarding the use of chemotherapy as part of multimodality treatment of malignant pleural mesothelioma (MPM). We aimed to determine whether, in those patients fit for chemotherapy, a delay in this treatment affected survival.
Materials and methods: We analysed postoperative variables of 229 patients undergoing either extrapleural pneumonectomy (EPP) (81 patients) or extended pleurectomy-decortication (EPD) (197 patients) for MPM at a single centre. There was no standard protocol for additional chemotherapy and varied with referral centre. Outcome was compared between 4 chemotherapy strategies: true adjuvant therapy, neo-adjuvant therapy, therapy reserved until evidence of disease progression in those otherwise fit in the post-operative setting, and those unfit for chemotherapy.
Results: There was no effect of the timing of chemotherapy on overall or progression free survival in patients fit enough for treatment ($p = 0.39$ and $p = 0.33$ respectively). However delaying chemotherapy until evidence of disease progression in patients with non-epithelioid disease had a detrimental effect on overall survival (OS), and on progression free survival (PFS) in lymph node positive patients (15.6 vs. 8.2 months $p = 0.001$, and 14.9 vs. 6.0 months $p = 0.016$). Further analysis of 169 patients receiving platinum/pemetrexed as first line treatment, showed similar results; there was no effect of the timing of chemotherapy on OS or PFS ($p = 0.80$ and $p = 0.53$ respectively) and an improved OS in patients with non-epithelioid disease, and improved PFS in those with lymph node metastases, if chemotherapy was given in the immediate adjuvant setting ($p = 0.001$ and 0.038) when therapy was not delayed until disease progression.
Conclusion: Our results suggest that the timing of additional chemotherapy may be important in those with a poorer prognosis on the basis of cell type and nodal stage. In these patients additional postoperative chemotherapy should not be delayed.

1. Introduction

Multimodality therapy for malignant pleural mesothelioma (MPM) including radical surgery with chemo-radiotherapy, has been associated with prolonged survival and disease control in selected patients, but the evidence for a long term survival benefit is inconsistent [1–9]. Chemotherapy, either in the neo-adjuvant, adjuvant or delayed palliative setting, has been shown to improve survival when compared with no chemotherapy at all [10]. There is little evidence regarding the optimal timing of additional chemotherapy, with some advocating treatment in the immediate post-operative setting, and others choosing to delay until progression. The benefits of neo-adjuvant chemotherapy include the use of response as a prognostic tool when selecting patients for radical surgery [11]. This may select those who will not have a prolonged survival, thus avoiding futile but morbid therapy. There is also the potential for tolerance of an increased number of cycles prior to surgery than in the adjuvant setting. The drawbacks include the risk

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Table 1
Chemotherapy treatment groups.

Group	Management	Definition
1	Adjuvant	Patients who received 'true' adjuvant chemotherapy in the absence of measurable disease with no delay between referral and the start of oncological work up and treatment
2	Neo-adjuvant	Patients who received neo-adjuvant chemotherapy and not adjuvant therapy
3	Expectant	Patients who were medically fit but did not receive adjuvant chemotherapy and in whom it was reserved for disease progression
4	Unfit	Patients who were unfit for chemotherapy in the adjuvant setting

of progression during chemotherapy, or severe toxicity, leaving the patient unsuitable for radical surgery [1–3,5–8,11].

A large proportion of patients may be unfit to proceed to adjuvant chemo-radiotherapy, particularly after extrapleural pneumonectomy (EPP) [11], decreasing the benefits seen with multimodality therapy [5,12,13]. The apparent benefit with adjuvant chemotherapy may be due to selection bias; only the fittest can receive the full regime, and will therefore have a survival benefit independent of therapy.

In some centres chemotherapy may be reserved until there is evidence of disease progression due to nihilism surrounding prognosis and the lack of subsequent therapy.

Our referral base for radical surgery encompasses a wide range of oncological practices reflecting the lack of an accepted protocol. This variation in practice has allowed us to compare the effect of timing of additional chemotherapy on the outcome of radical surgery, and to propose an optimum multimodality program.

2. Materials and methods

We retrospectively studied 294 consecutive patients from our prospectively updated institutional database who had undergone radical surgery for MPM, either by extrapleural pneumonectomy (EPP) or extended pleurectomy-decortication (EPD), at a single surgical centre, from 2000 to 2014. All patients had a macroscopic complete resection and underwent a systemic lymph node dissection at operation. We provide a surgical service for referring oncologists and physicians from throughout the United Kingdom. In total, in this cohort, we received patient referrals from 28 cancer centres. Surgery was performed by a group of 3 specialist surgeons at a single institution. During this period there was no standardised protocol for the provision of chemotherapy; therapeutic decisions were made without consultation with the surgical centre, at the discretion of the local team. All patients were referred back to their local team after surgery, with a request to consider additional treatment in the chemonaive patients. The rationale for giving or withholding chemotherapy in the neo-adjuvant or adjuvant setting was based on individual clinical preference and therefore practice varied with each referral centre.

Our institutional database and patient case notes were studied in order to determine the timing of chemotherapy. Referral hospitals were contacted for this information if it was not available from our centres' notes. If patients were not given chemotherapy in the adjuvant setting, a reason for this was sought. Patients were analysed in 4 categories determined by the timing of chemotherapy; group 1 Adjuvant, group 2 Neo-adjuvant, group 3 Expectant and group 4 Unfit for chemotherapy (Table 1).

Adjuvant chemotherapy was defined as chemotherapy treatment commenced immediately following the initial oncology review after surgery. All patients were referred to an oncologist at their original referral centre following outpatient surgical review at 4 weeks post surgery. Those receiving adjuvant therapy (group 1) were commenced on treatment within 3 months of surgery, following a CT scan demonstrating no evidence of disease progression. Expectant management (group 3) was defined as those patients who were seen by an oncologist at this same time point, and deemed to be medically fit for adjuvant therapy, yet the decision was taken to reserve chemotherapy until there was evidence of disease progression. Medical fitness was determined by the reviewing oncologist, and was based on performance status and renal function, and on whether there were any continuing post-operative complications which would preclude chemotherapy treatment. Patients were reviewed with a CT scan at a minimum of 3 monthly intervals to determine whether disease progression had occurred.

We also collected data on demographics, pre-operative blood test results, pathological diagnosis and stage. Cut offs for laboratory tests were used in line with the standard ranges determined by our haematology and clinical chemistry departments. Clinical disease progression was determined from records of regular outpatient attendances at our centre or from correspondence from referring centres. Time to disease progression was calculated from the date of surgery to first clinical or radiological finding of progression. Survival was calculated from time of operation to death or to the date of censoring at the last follow up appointment or last communication with the patient.

2.1. Platinum/pemetrexed chemotherapy only analysis

Due to the potential confounding nature of the differing chemotherapy regimes in use prior to the introduction of platinum/pemetrexed doublet as a standard of care in 2003/04, we undertook a sub-group analysis of patients from this cohort who received platinum/pemetrexed chemotherapy as first line neo-adjuvant or adjuvant therapy. The same methods of data collection and analysis were employed in this cohort of 226 patients as outlined above.

2.2. Statistical analysis

SPSS version 20 statistical software package was used for analysis. A test for normality of continuous data was performed after initial visual analysis of the data. Continuous data in this study were found not to be normally distributed in this study and as such were analysed using the Mann-Whitney *U* test. Categorical data were analysed using Chi-squared test, or Fisher's exact test when one or more of the cells had an expected frequency of five or less. A p value of less than 0.05 was considered to be statistically significant.

The Kaplan-Meier method with log rank test was used to compare for differences between groups in the progression free survival and overall survival analyses. The multivariable model was created using forward logistic regression within a Cox regression model. Variables with a p value of less than 0.1 were included in the model. In the multivariate analysis of chemonaive patients, Group 1 was compared with Group 3 only.

Ethical approval was not required as linked anonymised data was used in this study.

3. Results

3.1. Patients and demographics

Of the 294 patients studied, 65 patients were excluded from further analysis: 44 died before oncological assessment or commencement of chemotherapy (median overall survival 1.0 months); 14 progressed before adjuvant therapy was discussed or commenced (median time to progression 3.4 months); 5 chose not to undergo chemotherapy although they were deemed fit enough,