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# Four versus Six Cycles of Pemetrexed/Platinum as a First Line Treatment of Malignant Pleural Mesothelima: Results of a Randomized Phase II Study

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**Background:** Pemetrexed-platinum is the standard first line treatment of patients with malignant pleural mesothelioma (MPM). Optimal number of pemetrexed-platinum chemotherapy cycles is not yet known with certainty.
**Aim**: To compare 4 cycles versus 6 cycles of pemetrexed-platinum regimen as a 1st line treatment in MPM.
**Methods:** This was a randomized phase II study (1:1) which was conducted at a single institution. Arm A received 4 cycles of pemetrexed-platinum, while Arm B received 6 cycles. The 1ry outcome of the current study was overall survival. It was assessed through Kaplan-Meier survival estimates as well as a multivariate Cox regression model adjusted for other relevant baseline clinicopathological characteristics.
**Results:** A total of 60 patients were included into the current study (30 in each arm). Kaplan-Meier survival analysis according to the number of cycles of chemotherapy did not reveal a significant survival difference between both subsets (p = 0.194). Multivariate Cox regression analysis for factors affecting overall survival did not show an overall survival difference based on treatment arm (p = 0.105).
**Conclusions:** Six cycles does not appear to improve the overall survival of MPM patients compared to four cycles. Shorter course of treatment should be considered in resource-limited settings like Egypt.

***Keywords*:** Malignant pleural mesothelioma, 1st line chemotherapy, Pemetrexed
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## INTRODUCTION

Malignant pleural mesothelioma (MPM) is a hard-to-treat malignancy that arises from the pleural surfaces and is caused primarily by exposure to a number of occupational carcinogens (particularly asbestos) [1]. Recent efforts among industrialized countries were successful in limiting the mortality of this disease. Unfortunately, these efforts are still crippled in many developing countries where alarming increase in the incidence and mortality of this disease is observed [2].

Treatment of MPM is essentially through systemic chemotherapy. The role of additional locoregional treatment (e.g. surgery or radiation therapy) is not confirmed yet [3, 4]. The most accepted chemotherapy standard in this setting is pemetrexed-platinum combination based on a landmark phase III study published since more than a decade [5].

It is still not known with certainty if a longer course of chemotherapy would improve the survival of those patients. Particularly with concurrent evidence from non-small cell lung cancer suggesting equal survival of 4 versus 6 cycles of systemic chemotherapy among advanced non-small cell lung cancer patients.

Given the enormous cost repercussions associated with longer course of pemetrexed in those patients, it is reasonable to evaluate whether a more concise course of therapy would be equally effective to a longer course of therapy in the treatment of this disease.

The objective of this study was to compare the overall survival outcome of four versus six cycles of pemetrexed-platinum chemotherapy in MPM patients with MPM.

## METHODS

This was a randomized phase II study (1:1) which compared four versus six cycles of pemetrexed-platinum as 1st line treatment for patients with MPM. Arm A: 4 cycles; while arm B: 6 cycles of treatment.

The study was conducted at Ain Shams University hospitals and is registered at Clinicaltrials.gov with the record number of: NCT02497053. Appropriate ethical approval from the Faculty of Medicine - Ain Shams University of medicine was obtained and an informed consent was obtained from all patients.

Inclusion to this study was restricted to patients who did not experience progression after initial 4 cycles of treatment. It has thus to be noted that the analysis presented in the current study represents both per protocol as well as intention to treat analysis.

This study was planned as an exploratory, hypothesis-generating study; and thus, the reasonable sample size given the single center nature of the study conduct was 60 patients.

The chemotherapy regimen was pemetrexed-cisplatin in almost 80% of cases and pemetrexed-carboplatin in 20% of cases. Pemetrexed was administered at a dose of 500 mg/m$^2$.

The following information was collected prospectively in the current study: age at diagnosis, gender, residence, performance status, occupation, smoking, type of presentation, sidedness, histology, history of tapping and/or pleurodesis and whether surgical resection was done.

The primary outcome of the current study was overall survival. It was assessed through Kaplan-Meier survival estimates as well as a multivariate Cox regression model adjusted for other relevant baseline clinicopathological characteristics (including age, gender, performance status, smoking history, histology, treatment arm, and surgical treatment). These parameters were chosen because of their perceived prognostic relevance for malignant MPM patients.

## RESULTS

A total of 60 patients were included into the current study. The characteristics of the study population are shown in table 1.

**Table 1: Clinico-pathological and Epidemiological Factors**

| Factor | n. | % |
|---|---|---|
| **Gender** | | |
| Female | 32 | 53.3 |
| Male | 28 | 46.7 |
| **ECOG performance status** | | |
| 1 | 53 | 88.3 |
| 2 | 7 | 11.7 |
| **Residence*** | | |
| Endemic | 31 | 51.7 |
| Rural | 15 | 25 |
| Urban | 14 | 23.3 |
| **Employment** | | |
| Working | 29 | 48.3 |
| Not working | 31 | 51.7 |
| **Smoking** | | |
| No | 37 | 61.7 |
| Yes | 23 | 38.3 |
| **Presentation** | | |
| Cough | 5 | 8.3 |
| Dyspnea | 36 | 60 |
| Pain | 19 | 31.7 |
| **Sidedness** | | |
| Left | 23 | 38.3 |
| Right | 37 | 61.7 |
| **Histology** | | |
| Biphasic | 8 | 13.3 |
| Epithelial | 52 | 86.7 |
| **Tapping** | | |
| No | 15 | 25 |
| Yes | 45 | 75 |
| **Pleurodesis** | | |
| No | 53 | 88.3 |
| Yes | 7 | 11.7 |
| **Surgery**** | | |
| No | 50 | 83.3 |
| Yes | 10 | 16.7 |

**ECOG**: Eastern Cooperative Oncology Group; *Endemic areas include: Shoubra and Helwan; **Surgery done was pleurectomy/decortication.

Females represent 53.3% of the entire study population. Mean age was 51.52 (SD: 9.236). Stratified by treatment arm, there was no difference between both arms with regards to mean age (p = 0.793). All patients have ECOG performance status <3. Half of the patients were employed at the time of diagnosis and 38.3% had a positive history of smoking. The majority (61.7%) of patients presented with right side disease and epithelioid histology was predominant (86.7%). Only 16.7% of patients underwent surgery (pleurectomy/decortication). Comparing the two arms of the study together, there was no statistically significant difference in gender, performance status, smoking history, residence or side of the tumor. There was, however, a statistically significant difference with regards to histology (more patients in the 6-cycle arm have epithelioid histology; p = 0.023).

All patients were followed till death and Kaplan-Meier analysis of overall survival according to the number of cycles was conducted (figure 1).

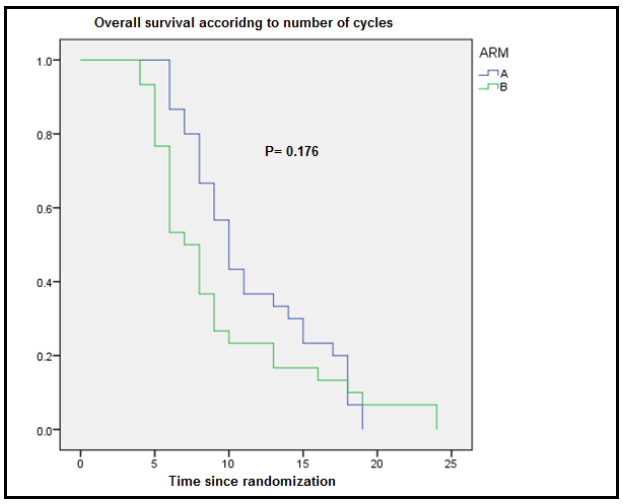


**Figure-1: Kaplan-Meier overall survival curves according to number of cylces (**Arm A: 4 cycles; Arm B: 6 cycles**).**

There was no evidence of a survival difference based on the number of cycles (p = 0.176). Median overall survival was 11.4 months for the 4-cylces arm versus 9.2 months for the 6-cycles arm.

An additional assessment of overall survival in a multivariate Cox regression analysis adjusted for factors illustrated in the methodology section did not show any evidence of a survival benefit based on the number of cycles (p = 0.105). The only factor which was associated with better overall survival in multivariate analysis was older age (p = 0.038) (table 2).

Partial response (as a best overall response) was reported in 10% of the 4-cycle arm versus 16.7% in the 6-cycle arm group. Six-month progression-free survival was 28.5% among the 4-cycle arm versus 26.2% among the 6-cycle arm.

Generally, there was no difference in the rate of grade 3 toxicities between the two treatment arms (p = 0.274).

**Table 2: Multivariate Cox regression analysis of factors affecting overall survival**

| Parameter | HR (95% CI) | P value |
|---|---|---|
| Age (continuous variable) | 0.967 (0.936-0.998) | 0.038 |
| Gender | | |
| Male | Reference | 0.579 |
| Female | 1.258 (0.559-2.828) | |
| Performance status | | |
| 2 | Reference | 0.660 |
| 1 | 0.804 (0.304-2.125) | |
| Smoking | | |
| Yes | Reference | 0.393 |
| No | 0.690 (0.295-1.615) | |
| Histology | | |
| Epithelioid | Reference | 0.083 |
| Biphasic | 2.277 (0.898-5.775) | |
| Treatment arm | | |
| 6 cycles | Reference | 0.105 |
| 4 cycles | 0.601 (0.324-1.113) | |
| Surgery | | |
| Yes | Reference | 0.81 |
| No | 1.101 (0.503-2.407) | |

## DISCUSSION

The current study provides an assessment of the impact of number of cycles on the outcomes of patients with MPM referred for pemetrexed-platinum chemotherapy. It shows clearly that there is no superiority for a longer course of therapy compared to shorter course of therapy and that, in a resource-limited setting like Egypt, the duration of pemetrexed-platinum chemotherapy should be revisited.

The current study has a number of limitations that need to be acknowledged. First, the relatively small sample size of the study might have obscured small survival differences from being demonstrated. This indicates the need to retest the same hypothesis in a larger, potentially multicentric cohort of patients. Second, while overall survival was clearly non-significant between treatments arms, progression-free survival was not assessed nor reported in the current study. The reason for this partially stems from the difficulty with regards to assessing response using standard response evaluation criteria (RECIST) [6]. This highlights the need to develop a more reliable and predictable response evaluation criteria for patients with MPM. Third, given the fact that almost 17% of patients underwent subsequent surgery, this might have confounded the overall survival results. This was accounted for in the multivariate analysis by incorporating surgery as one of the factors and this did not change the final survival results of the study. Fourth, while the current results are relevant in the setting of pemetrexed-platinum doublets, the results might not be relevant in view of the more recent results suggesting that the addition of bevacizumab might improve the outcomes of unresectable MPM patients [7].

Given the recent encouraging results of immune checkpoint inhibitors (e.g. pembrolizumab or nivolumab) in the treatment of MPM patients and the fact that these agents are usually administered till progression, it becomes prudent to reassess the same concepts in the setting of treatment with these agents [8].

The current study has major cost implications, particularly in resource-limited countries, which are unfortunately also most commonly plagued by this disease. This is apparent given the escalating costs of healthcare for oncology patients particularly drug costs.

The current study provides also a unique opportunity to study disease characteristics and outcome parameters among patients with MPM in Egypt which has a notoriously high prevalence of this disease. It is interesting to note that within the current cohort of patients, younger age was associated with worse overall survival in multivariate analysis. This point needs to be further evaluated on the biological and clinical levels.

### *Conclusion*

The current study provides a thought-provoking idea suggesting that shorter course of therapy might be as effective as longer course of therapy among patients with MPM. Larger multicentre studies are needed to overcome the limitations of the current study and to further confirm this concept.

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**Conflict of Interest:** None.

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