Survival in Good Performance Malignant Pleural Mesothelioma Patients; Prognostic Factors and Predictors of Response

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Abstract

**Purpose:** Malignant pleural mesothelioma (MPM) has a poor prognosis in general. Here we sought to evaluate prognostic factors and predictors of response to chemotherapy in good performance (PS=0-I) patients. **Methods:** We retrospectively reviewed our database and enrolled patients with MPM who received platinum containing chemotherapy (2012-2014). Clinico-pathological and laboratory data were retrieved and Cox and logistic regression multivariate analyses (MVA) were respectively used to identify predictors of survival and response to chemotherapy. Comparison of good vs poor performance status (PS≥II) was accomplished using the Chi (X²) test. Kaplan–Meier survival curves were also obtained and propensity-score matching was performed for survival comparison. **Results:** Among 114 patients listed during the study period, 82 had good PS=0-I (median age 45years, 43 men, 30 smokers, median weight=77Kg, pretreatment haemoglobin (Hb) level=12g/dL, platelet count=372,000/μL, leukocytes=9,700/μL, neutrophils=6,100/μL, lymphocytes=1,890/μL and neutrophil/lymphocyte ratio (NLR)=3.60 ). Some 65 had asbestosis, 23 had chronic disease, 55 (67.1%) were responders to platinum containing first line chemotherapy. Median-OS and PFS in good PS cases were 17 and 9 months, respectively, as compared to 16 and 8 months for the poor PS group. After matching, better OS was observed among good PS vs poor PS patients (p=0.024) but there was no PFS difference (p=0.176). Significant decrease in PFS was observed among those with advanced nodal N disease (median PFS in N0 and N+ was 10 and 5 months, respectively), non-responders (p=0.012), NLR (p=0.026) and smokers (p=0.07) adversely affected the prognosis. The only predictor of response was absence of metastasis (M0; p=0.04). **Conclusions:** In addition to previously recognized factors, like nodal status, response, smoking and NLR, better median survival was evident in our patients with a good PS. Early detection before development of metastasis warrants greater focus to allow better responses to be obtained.

**Keywords:** mpm-predictors-response-performance

Introduction

Malignant pleural mesothelioma (MPM) is a rare tumor arising from pleural mesothelial cells and is often linked to asbestos exposure. It usually carries a poor prognosis, with a median survival of 9 to 12 months from the diagnosis. (Curran et al., 1998) The mainstay of treatment of advanced stages of MPM is chemotherapy alone, or in combination with surgery and/or radiotherapy for resectable disease. Since 2003, pemetrexed and cisplatin combination has been the standard first-line treatment upon appearance of phase III trial results that revealed almost a 3 month median survival improvement over treatment with cisplatin alone. (Vogelzang et al., 2003) Two groups created prognostic scores to better select patients for more aggressive treatment; Cancer and Leukemia Group B (CALGB) and European Organization for Research and Treatment of Cancer (EORTC). The CALGB study included 309 patients with MPM and PS of 0 to II between 1984 and 1994. Poor prognostic factors for survival were pleural disease extent, higher lactate dehydrogenase (LDH>500 UI/L), poor PS, higher platelet count (> 400,000), non- epithelial histology, and older age (>75 years). MVA demonstrated that advanced (N) status (p=0.015), being a non-responder (p=0.001), NLR (p=0.015) and smoking (p=0.07) adversely affected the prognosis. The only predictor of response was absence of metastasis (M0; p=0.04). Albeit both studies identified histology and PS as the two main prognostic factors in patients with MPM, these analyses included patients with a range of tumor stages at diagnosis, the majority of whom underwent major surgery and their treatment predated the use of the current...
chemotherapy regimens.

Since the beginning of routine use of chemotherapy regimens, including pemetrexed as first-line therapy, only one new prognostic index for OS has been created that is based on a retrospective analysis of 283 patients who were treated with chemotherapy alone between 2007 and 2013. PS, histology, stage (I-III versus IV), and pemetrexed-based chemotherapy were independent prognostic factors for survival; however, no factors were analyzed for association with chemotherapy.(van Meerbeeck et al., 2005) We therefore undertook this study to identify prognostic factors in a more uniform, contemporary cohort of nonsurgical patients treated with current chemotherapy regimens, as well as to identify factors that might correlate with clinical benefit from chemotherapy.

**Materials and Methods**

**Patients and Data Collection**

We retrospectively reviewed our National Cancer Institute – Thoracic Department (NCI-TD) database and patients’ medical records and enrolled patients with pathologically confirmed MPM and European Cooperative Oncology Group scale ECOG-PS=0-I who underwent evaluation and treatment between January 2012 and December 2014 and then compared them to those with poor PS(ECOG PS≥II) during the same period. We excluded patients treated at another hospital, peritoneal mesothelioma patients, and those with lost follow-up.

Patients who had a surgical procedure for staging or diagnostic surgical procedure or for palliative procedure for pleural effusion were included but those who underwent pleural decortication or extrapleural pneumonectomy were excluded. Patients’ demographics, clinical, radiological and pathological data were retrieved from the medical records. Analyzed variables were age, weight, gender, smoking status, comorbidities, documented exposure to asbestos, different symptoms, Tumor(T), Nodal (N), Metastasis(M) and International Mesothelioma Interest Group(IMIG) stages, different pre-treatment laboratory values, including pretreatment haemoglobin (Hb), white blood cells(WBCs), platelets count, neutrophils, lymphocytes, neutrophil/lymphocyte ratio (NLR) and pathology. The normal ranges for hemoglobin, platelets, WBCs, neutrophils count, and lymphocytes count were noticed as regarding median weight(77 Kg (65-88)), Hb=12g/dL (10.8-12.9), platelet= 372,000 /μL (306,000-473,000), TLC=9,700/μL(4,400-7,250), neutrophil=6,100/μL (4,400-7,250), lymphocyte=1,900/μL(1,000-2,400), NLR=3.60(2.40-6.00) pretreatment (Table 1). Forty three were men, 30 were smokers, 65 had asbestosis, 23 had chronic disease and 55 (67.1%) were responders to chemotherapy.

On comparing good vs. poor PS; significant differences were noticed as regarding median weight(77 vs. 88.5 Kg), male gender(52 vs. 72%), presence of grade 2 chest pain(46 vs. 0%), anorexia(32 vs. 50%), pleural effusion(84 vs. 97%), median pretreatment Hb (12 vs. 11.2), platelets(372,000 vs. 316,000), lymphocytes (1,900 vs. 1,000) and NLR(3.65 vs. 5.3) respectively. (Table1)

**Results**

114 patients with MPM were included during the study period. Patients with good PS(0-I) were 82 versus 32 with poor PS(≥II). Among good PS patients, the median age was 45 years (IQR; 38.3-55), weight 77 Kg (65-88), Hb=12g/dL (10.8-12.9), platelet= 372,000 /μL (306,000-473,000), TLC=9,700/μL(4,400-7,250), neutrophil=6,100/μL (4,400-7,250), lymphocyte=1,900/μL(1,000-2,400), NLR=3.60(2.40-6.00) pretreatment (Table 1). Forty three were men, 30 were smokers, 65 had asbestosis, 23 had chronic disease and 55 (67.1%) were responders to chemotherapy.

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**Survival, Univariate and Multivariate analysis:**

Among good PS cohort; 1-year OS and PFS were 73.1% and 32.9% respectively with median follow-up time of 16 months. Median OS and PFS were 17 months (95%CI: 14.1-19.9) and 9 months (95%CI: 7 - 11.03) respectively (Figure1) while in poor PS cohort median OS and PFS was 16 months (95%CI: 12.7 - 19.3) and 8 months (95% CI: 6.6 - 9.4) respectively. No statistical significant difference in OS (p=0.383) between good and poor PS while there is a trend toward significance regarding PFS (p=0.121). However, after the propensity score matching,
better OS was observed in good PS with median OS of 19 months vs. 16 months in poor PS (p=0.024) while no difference in PFS (p=0.176; Figure 2)

Cox proportional hazards model was conducted on different clinico-demographic and pathological data and revealed that advanced nodal (N) disease (median PFS in N0 and N+ were 10 and 5 months respectively; p= 0.07), non-responder (p=0.012), NLR (p=0.026) and epithelial pathology (p=0.062) were associated with significant decrease in PFS. Multivariate analysis demonstrated that advanced N status (p=0.015), non-responder (p<0.001), NLR (p=0.015) and smoking (p=0.07) adversely affecting prognosis. (Table 2)

Table 1. Patients Characteristics among Our Cohort Prior and after Match (Good vs Poor PS)

| Patients characteristics (n=114) | Frequency (%), Median (IQR) | P value |
|----------------------------------|-----------------------------|---------|
| Age; yrs                         | 45 (22-68) vs 48 (40.3-57.8) | 0.13    |
| Male gender                      | 43 (52.4) vs 23 (71.9)      | 0.059   |
| Weight; Kg                       | 77 (65-88) vs 85.8 (78.3-95.5) | 0.001   |
| Chronic disease                  | 23 (28) vs 30 (10.31)       | 0.735   |
| Asbestos                         | 65 (79.3) vs 31 (65.6)      | 0.128   |
| Smokers                          | 30 (36.6) vs 12 (37.5)      | 0.928   |
| Dyspnea                          | 76 (92.7) vs 29 (90.6)      | 0.714   |
| Chest pain                       | 72 (87.8) vs 26 (81.3)      | 0.365   |
| Grade 2 Chest pain               | 35 (45.5) vs 0 (0)          | 0.001   |
| Cough                            | 44 (53.7) vs 20 (62.5)      | 0.393   |
| Fatigue                          | 53 (64.6) vs 23 (71.9)      | 0.461   |
| Anorexia                         | 19 (23.2) vs 16 (50)        | 0.005   |
| Pleural effusion                 | 69 (84.1) vs 31 (96.9)      | 0.063   |
| Pleural thickening               | 78 (95.1) vs 31 (96.9)      | 0.881   |
| T4 stage                         | 14 (17.1) vs 5 (15.6)       | 0.852   |
| N+                               | 27 (32.9) vs 8 (25)         | 0.41    |
| M+                               | 10 (12.2) vs 5 (15.6)       | 0.626   |
| IMIG stage III/IV                | 59 (72) vs 20 (62.5)        | 0.326   |
| Pretreatment hemoglobin; g/dL    | 12 (10.8-12.9) vs 11.15 (10-12) | 0.043   |
| Platelets; /μL                   | 372,000 (306,000-473,500) vs 316,000 (214,000-464,000) | 0.054 |
| WBC; /μL                         | 9,660 (7,498-12,000) vs 10.6 (925,000-12,000) | 0.113 |
| Neutrophils; /μL                 | 6,100 (4,400-7,250) vs 6,200 (4,550-7,275) | 0.762 |
| Lymphocytes; /μL                 | 1,850 (1,000-2,400) vs 1,000 (800-1,800) | 0.001 |
| NLR                              | 3.6 (4.31-2.76) vs 5.3 (3.97-8.77) | 0.001 |
| Epithelial histology             | 49 (59.8) vs 18 (56.3)      | 0.566   |
| Median OS(months;IQR)            | 17 (14-19.9) vs 16 (12.7-19.3) | 0.383 |
| Median PFS                       | 9 (7-11) vs 8 (6.6-9.6)      | 0.121   |
| Median TTP                       | 10 (8.2-11.8) vs 8 (5.8-10.2) | 0.258 |
| Median Follow up                 | 16 vs 16.5                  | ....    |

After Propensity score Match(n=58)

| Age; (>Median 45 yrs) | 13 (44.8%) vs 14 (48.3%) | 0.792   |
| Male gender           | 18 (62.1%) vs 20 (69%)    | 0.581   |
| Weight; median 77kg   | 16 (55.2%) vs 21 (72.4%)  | 0.172   |
| Chronic disease       | 10 (34.5%) vs 9 (31%)     | 0.78    |
| Asbestos              | 25 (86.2%) vs 20 (69%)    | 0.115   |
| Smokers               | 10 (34.3%) vs 11 (37.9%)  | 0.785   |
| IMIG stage IV         | 7 (24.1%) vs 9 (31%)      | 0.52    |
| Pretreatment hemoglobin; g/dL | 11.9 (10.6-12.9) vs 11 (10-12) | 0.123 |

Table 1. Continued

| Patients characteristics (n=114) | Frequency (%), Median (IQR) | P value |
|----------------------------------|-----------------------------|---------|
| Platelets; /μL                   | 369,000 (328,000-482,000) vs 321,000 (214,000-549,000) | 0.146   |
| WBC; /μL                         | 11,000 (9,000-12,150) vs 10.2 (8,900-12,000) | 0.732   |
| Neutrophils; /μL                 | 6,600 (3,800-7,750) vs 6,100 (4,450-6,850) | 0.544   |
| Lymphocytes; /μL                 | 1,800 (1,000-2,300) vs 1,000 (800-1,800) | 0.013   |
| NLR                              | 3.92 (2.60-6.20) vs 5.30 (3.74-9.23) | 0.027   |
| Epithelial histology             | 19 (65.5%) vs 16 (55.2%) | 0.421   |

LN, lymph node; N, nodal stage; M, metastasis stage; IMIG, International mesothelioma Interest Group staging; WBCs, white blood cells; OS, overall survival; IQR, inter-quartile range; PFS, progression free survival; TTP, time to progression

Figure 1. OS and PFS among Good PS

Figure 2. Matched Good vs Poor PS
Response to chemotherapy in good PS cohort

92.7% of good PS had documented at least 2 chemotherapy cycles while 76.3% had 3 or more chemotherapy cycles.

Patients with partial or complete response (PR/CR) had a better OS compared to non-responders (stable or progressive disease (SD/PD)) with a median of 21 vs. 15 months respectively (p=0.026). Similarly, chemotherapy responders (PR/CR) had a higher PFS compared to the remaining (SD/PD) with median PFS 12 vs. 6 months respectively (p=0.007; Figure 3).

Logistic regression model was created to determine factors predicting response to chemotherapy and revealed that absence of asbestosis (p=0.05), absence of fatigue (p=0.03), absence of metastasis (p=0.04), lower platelets count (p=0.05) to be predictors of response in univariate analysis. However, MVA showed only absence of metastasis (M0;p=0.047) to be the significant predictor of response.

Table 2. Predictors of Progression Free Survival among Our Cohort (n=82)

| Independents Variables | Univariate Analysis | Multivariate Analysis |
|------------------------|--------------------|----------------------|
| Age* | 1.01 (0.99-1.03) | 0.517 |
| Weight* | 1.01 (0.99-1.03) | 0.119 1.01 (0.99-1.03) | 0.164 |
| Gender | | | |
| Female (n=39) | Reference | |
| Male (n=43) | 1.26 (0.81-1.97) | 0.313 |
| Presence of Chronic disease | | | |
| No (n=59) | Reference | |
| Yes (n=23) | 1.31 (0.79-2.16) | 0.294 |
| Asbestosis | | | |
| No (n=17) | Reference | |
| Yes (n=65) | 1.11 (0.65-1.90) | 0.715 |
| Smoking | | | |
| No (n=52) | Reference | Reference |
| Yes (n=30) | 1.41 (0.88-2.27) | 0.153 1.59 (0.96-2.63) | 0.073 |
| Dyspnea | | | |
| No (n=6) | Reference | |
| Yes (n=76) | 1.24 (0.53-2.89) | 0.616 |
| Chest pain | | | |
| No (n=72) | Reference | |
| Yes (n=38) | 0.86 (0.44-1.67) | 0.65 |
| Cough | | | |
| No (n=44) | Reference | |
| Yes (n=28) | 1.13 (0.73-1.76) | 0.589 |
| Fatigue | | | |
| No (n=29) | Reference | |
| Yes (n=53) | 1.30 (0.81-2.07) | 0.276 |
| Anorexia | | | |
| No (n=63) | Reference | |
| Yes (n=19) | 1.01 (0.59-1.71) | 0.981 |
| Effusion | | | |
| No (n=13) | Reference | |
| Yes (n=69) | 1.07 (0.58-1.99) | 0.826 |
| Mediastinal LN ¶ | | | |
| No (n=48) | Reference | |
| Yes (n=34) | 1.37 (0.88-2.14) | 0.169 |
| T stage | | | |
| T1,T2,T3 (n=68) | Reference | |
| T4 (n=14) | 1.25 (0.70-2.24) | 0.452 |
| N stage | | | |
| N0 (n=55) | Reference | Reference |
| N+ (n=27) | 1.50 (0.94-2.40) | 0.071 1.87 (1.13-3.09) | 0.015 |
| M stage | | | |
| M0 (n=67) | Reference | Reference |
| M1 (n=15) | 1.50 (0.88-2.57) | 0.134 1.02 (0.58-1.81) | 0.936 |

Table 2. Continued

| Independents Variables | Univariate Analysis | Multivariate Analysis |
|------------------------|--------------------|----------------------|
| Response | | |
| Non responsive (SD/PD) n=27 | Reference | Reference |
| Responsive (PR/CR) n=55 | 0.55 (0.34-0.88) | 0.012 0.35 (0.20-0.62) | <0.001 |
| Pretreatment Hb | 0.96 (0.87-1.07) | 0.469 |
| Platelet* | 1.01 (0.99-1.01) | 0.307 |
| TLC* | 1.03 (0.97-1.10) | 0.344 |
| Neutrophils* | 1.03 (0.92-1.14) | 0.643 |
| Lymphocytes* | 1.01 (0.99-1.02) | 0.204 |
| Neutrophils/ Lymph Ratio (1.001-1.030) | 0.026 1.010 | 0.015 |
| Pathology | | |
| Epithelial (n=49) | Reference | Reference |
| Sarcomatoid/ Mixed (n=33) | 0.64 (0.40-1.02) | 0.062 0.81 (0.49-1.34) | 0.422 |

Figure 3. Response To Chemotherapy among Good PS

Response to chemotherapy in good PS cohort

92.7% of good PS had documented at least 2 chemotherapy cycles while 76.3% had 3 or more chemotherapy cycles.

Patients with partial or complete response (PR/CR) had a better OS compared to non-responders (stable or progressive disease (SD/PD)) with a median of 21 vs. 15 months respectively (p=0.026). Similarly, chemotherapy responders (PR/CR) had a higher PFS compared to the remaining (SD/PD) with median PFS 12 vs. 6 months respectively (p=0.007; Figure 3).

Logistic regression model was created to determine factors predicting response to chemotherapy and revealed that absence of asbestosis (p=0.05), absence of fatigue (p=0.03), absence of metastasis (p=0.04), lower platelets count (p=0.05) to be predictors of response in univariate analysis. However, MVA showed only absence of metastasis (M0;p=0.047) to be the significant predictor of response.
Discussion

Many studies postulate that good PS is considered as a good prognostic factor and predicts better survival in patients with MPM, such as CALGB and EORTC indices in addition to other prognostic factors. However they had worked on selected patient in clinical trials, patients undergoing extensive surgery, and chemotherapy patients who have a favorable prognosis and could tolerate and potentially benefit from a more aggressive combined modality treatment before the use of pemetrexed and other new current regimens became routine. In this study we sought to investigate different clinico-demographic and prognostic criteria among this good PS cohort. (Billé et al., 2016; Edwards et al., 2003; Pinato et al., 2013; Suzuki et al., 2014) Our study, that examined a relatively uniform cohort of patients with unresectable disease who received platinum based regimens as a standard first-line treatment, confirms that some elements of the CALGB and EORTC prognostic scoring systems correlate with survival in this patient population as well.

The most prevalent symptoms and histology among our cohort were chest pain and dyspnea and epithelial pathology that are in concordance with many series. (Elkasem et al., 2017a, 2017b; Najmi et al., 2014; Shokralla) Asbestosis was evident in 79.3% and more than two-thirds of the cases aged between 40 and 59 years, that is not consistent with prior series (Borasio et al., 2008) signifying early disease onset among our population, that might be related to heavy asbestos exposure. This heavy exposure proved to be as important as long term low asbestos dose exposure with or without higher genetic predisposition. (Bianchi and Bianchi, 2007; Metintas et al., 2008).

Median OS was 17 months which is better than recently published series from Memorial Sloan Kettering Cancer Center who reported median OS for all patients was 13.4 months. However they had 82% of their cases with stage III or IV MPM vs. 72% among the current series 8.

Histology carries a significant difference in survival with epithelial MPM being the best in term of prognosis in contrast to either sarcomatoid or mixed MPM, (Edwards et al., 2003; Flores et al., 2007) however; we couldn’t prove that but furthermore there was a better survival in non-epithelial histology. This may be explained in part by high prevalence of advanced stage among our epithelial MPM cohort (IMIG stage 4 was present in 34.7 vs. 24.2% in non-epithelial cohort).

Lower NLR was associated with better survival that was evident in in meta-analysis conducted by Templeton et al., (2014) on MPM and also in other thoracic malignancies as esophageal cancer reported by Sharaia et al., (2011) who reported that NLR reflect the systemic inflammatory response created by a tumor and is possibly predictive of tumor aggressiveness and propensity for metastasis.

Advanced nodal (N) stage and smoking were linked to poor survival in MPM and many other thoracic malignancies e.g. lung cancer. (Rahouma et al., 2015; Richards et al., 2010; Shokralla and Rahouma, 2016).

Chemotherapy was designated to down stage, cure cancer, decrease disease progression or palliate symptoms so, it is logic that absence of response to chemotherapy will be associated with disease progression and hence poor survival and this was evident among our cohort and run in parallel with previously published data (Blayney et al., 2012).

In our previously published series on non-epithelial MPM, presence of asbestosis was the only predictor of poor response to chemotherapy which is in concordance with our cohort results (Shokralla et al., 2016) however this significance disappeared in the multivariate analysis signifying that it is not an independent predictors among our cohort that involved both epithelial and non-epithelial histology.

Absence of metastasis (M0) was the significant predictor of response to chemotherapy and this may be explained by the fewer tumor loads that chemotherapy has to face.

Despite some limitations and confounding factors, our analysis expands on prior studies of prognostic factors in MPM. In particular, we identified that absence of metastasis to be associated with clinical benefit from first-line chemotherapy and that nodal (N) status, chemotherapy responder, NLR and smoking status are prognostic for survival in the multivariate analysis. Although future studies evaluating the biology of MPM as well as the prognostic value of tumor volume measurements may improve therapy selection, our results define measurable clinical factors that can help direct patient treatment easily.

In conclusion, pretreatment NLR is a potential prognostic marker for progression and death in treated MPM patients. Better response to chemotherapy treatment predicts better PFS. Smoking and Advanced N stage hinder the survival among good PS MPM patients. Better median survival was evident in patients with good PS. Early detection prior to development of metastasis is warranted to get better response.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Ethical approval

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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