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The relationship between treatment cost and prognosis of malignant pleural mesothelioma in Turkey

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Abstract:

BACKGROUND: Malignant pleural mesothelioma (MPM) is endemic in the population exposed to asbestos and has high health-care cost with a limited life expectancy. The aim of this study is to evaluate the relationship between cost according to treatment type and prognosis in MPM.

MATERIALS AND METHODS: A total of 309 patients with MPM were evaluated. Direct medical costs were estimated as the sum of hospital bills attributed to MPM for all patients followed up from hospital application to death. Three treatment strategies were compared to each other in terms of survival and median incremental costs per month gained cost.

RESULTS: The mean age of the patients was 63.2 ± 11.2 years. The total median costs per patient and median survivals were $1838 and 5 months, $10,540 and 11 months, and $17,022 and 22 months for the best supportive care, the chemotherapy, and the multimodality groups, respectively. Factors affecting the cost of MPM were histology, treatment type, received second- and third-line chemotherapy, and number of hospitalization.

CONCLUSION: MPM has a limited survival time despite treatment, and treatment cost is relatively high by prolongation of lifetime. Chemotherapy and multimodality approaches seem to be cost-effective until to be find more effective targeted therapies.

Keywords:

Cost analysis of mesothelioma, direct cost of mesothelioma, mesothelioma treatment

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Introduction

Malignant pleural mesothelioma (MPM) is an aggressive tumor and remains a significant public health concern because of its poor prognosis and increasing incidence.[1] Most of the patients are exposed to asbestos. Although exposure to asbestos ended in the west, heavy exposure still continues in many developing countries, including Russia, China, India, Brazil, and Kazakhstan.[2] Because of latency period of disease, in both developed and developing countries, mesothelioma peak will typically occur over the next decade when projections of the future burden of disease have been carried out.[3] Besides its industrial use, there is an environmental asbestos exposure in some parts of the world, including Turkey. Asbestos has been widely used in the rural area of Turkey for whitewashing, plastering, insulation and waterproofing, floor and roof covering, baby powdering, and pottery in the past.[4] Although the use across the country has been greatly reduced, the MPM incidence has not yet declined due to past exposure. Environmental exposure is as effective as the occupational exposure in terms of the mesothelioma risk.[4-6]

There is currently no universally accepted standard treatment for MPM. The combination of cisplatin and pemetrexed

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is widely used for the systemic treatment of advanced stage disease.[7] There is no targeted therapy yet. The combination of surgical resection, adjuvant radiation therapy, and/or neoadjuvant/adjuvant chemotherapy in multimodality treatment approaches is improved overall survival and locoregional control in early-stage disease.[8,9] The overall survival of MPM patients varies among these treatment schedules. The median survival of patients receiving best supportive care (BSC) is 7 months and those receiving chemotherapy is about 12 months, whereas the survival of patients with multimodality treatment is 14–36 months.[7-11] However, these intensive therapies are brought out significant health-care expenditure with a limited life expectancy. The economic burden of MPM is a significant concern for asbestos-exposed population. In response to the high cost of MPM treatment relative to their perceived benefits, health insurance beneficiaries with MPM, physicians, and government are faced with difficult decisions regarding the allocation of health-care resources. Studies on MPM cost can inform researchers and policymakers and be used for health economic modeling.

The aim of this study is to evaluate the relationship between health-care cost and prognosis according to treatment types and factors affecting health-care cost in MPM patients who exposed to asbestos environmentally in Turkey.

Materials and Methods

Patients

A total of 309 patients were histologically diagnosed as MPM and treated to international standards at Chest Disease Department of Eskisehir Osmangazi University Hospital in Turkey between October 2005 and September 2015. Our clinic is a reference center for MPM and lung cancer in the central part of Anatolia. Thirty-four patients were excluded from the cost analyses because of insufficient follow-up. The demographics and health-care costs of 275 patients with MM were obtained from hospital records. The Ethical Committee of our university approved the study.

Clinical data including age, gender, comorbidities, histology, stage, Karnofsky Performance Status (KPS), treatment history, and survival characteristics were collected for all the patients. A history and physical examination, complete blood count and differential, chemistry panel, electrocardiogram, chest radiograph, chest and abdominal computed tomography (CT) scans, positron-emission tomography (PET)–CT scan, biopsy, and histological workup were performed at baseline for all patients. Besides, detailed pulmonary function tests, cardiac evaluation, and brain magnetic resonance imaging were performed when necessary. The patients were staged according to the International Mesothelioma Interest Group staging system.[12]

Treatment

After diagnosis, the BSC, chemotherapy, surgery, radiotherapy (RT), or combination therapies were applied to the patients who gave written informed consent. BSC was given to all patients right after the diagnosis. The chemotherapy regimen was platinum compounds in combination with pemetrexed in this study. Pemetrexed 500 mg/m^2 was given intravenously on day 1, followed by cisplatin 80 mg/m^2 or carboplatin 300 mg/m^2, intravenously on day 1, which was repeated every 21 days. Chemotherapy was given for 4–6 cycles or until disease progression, unacceptable adverse events, or patient unwillingness to chemotherapy. In addition, the use of any second/third-line chemotherapy was recorded. Most of the chemotherapy regimens for the second and third lines were gemcitabine and vinorelbine, respectively, in this study.

Multimodality treatment was accepted combination of surgery, chemotherapy, and RT. These multimodality strategies were to perform extrapleural pneumonectomy (EPP), adjuvant hemithoracic irradiation (high dose or intensity-modulated radiation treatment [IMRT]) and chemotherapy or to perform pleurectomy and decortication (P/D), chemotherapy, and prophylactic irradiation to the incisions. However, in patients with R2 resections in this group, targeted irradiation was performed to gross tumor sites. Irradiation was accepted as a modality in multimodality approach if it was high-dose hemithoracic irradiation or IMRT following EPP or extended P/D and targeted radiation for recurrence sites following P/D.

The history and physical examinations were performed every 21 days in chemotherapy and multimodality groups. The complete blood count and differential and chemistry panel were performed weekly during treatment. The tumor response to chemotherapy was evaluated by CT scans and obtained every two or three cycles of chemotherapy. Thereafter, CT scans were performed at 3 monthly intervals until disease progression. PET–CT scan was revealed when indicated. In the BSC group, the history, physical examination, blood count, chemistry panel, and chest radiograph were performed every month.

Cost assessment

The Social Security Institution covers all health expenditures including cancer treatment for all citizens in Turkey. Direct medical costs were estimated as the sum of hospital bills attributed to MPM for all patients followed up from hospital application to death. Indirect cost was not included in this study. Any hospital

bill nonrelated to MPM was excluded from the cost analysis.

The phases of care were divided into three periods as diagnosis, treatment, and terminal phase in chemotherapy and multimodality groups. Diagnosis phase was defined as the time from admission to treatment and included all diagnostic and staging workups till treatment. Treatment phase was defined as the time from diagnosis to progression and end of active anticancer treatment. Terminal phase was defined as the time from interruption of active anticancer treatment to death. In the BSC group, it was divided into two periods as diagnosis and postdiagnosis phases.

The costs were stratified by age (<65 and ≥65), gender, histology (epithelioid and nonepithelioid), stage (I–II and III–IV), KPS (≤70 and >70), and treatment (BSC, chemotherapy, and multimodality). These prices were converted from Turkish Lira to US Dollar using average exchange rate of each study year between 2005 and 2015.

Statistical analyses

Data were collected, analyzed, and evaluated in the Lung and Pleural Cancers Research and Clinical Center of Eskisehir Osmangazi University. Statistical analyses were performed using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA) 15.0 program. The cost of each patient was calculated by summing the costs of all parameters from diagnosis to death. The suitability to normal distribution of cost variable was examined by the Kolmogorov–Smirnov test and graphs. The cost variable did not show normal distribution. To compare the study groups, Chi-square test was performed for qualitative data and Mann–Whitney U-test or Kruskal–Wallis test with Bonferroni correction was performed for quantitative data. The median survival times with 95% confidence intervals were estimated for each group using the Kaplan–Meier method. All of the patients were followed until death. The median survival times were compared between the groups using log-rank test. Three treatment strategies were compared to each other in terms of survival and median incremental costs per month gained cost. To calculate the incremental cost per month gained, the median survival time difference of the groups was divided by the median cost difference.[13] Finally, we identified the factors affecting the cost of MPM. The logarithm of the cost variable was taken to provide normal distribution. Univariate analysis was performed to determine the independent variables affecting the dependent variable obtained. A multivariable linear regression model was constructed with $P < 0.10$ independent variables in univariate analysis. $P \leq 0.05$ was considered statistically significant in all comparisons.

Results

A total of 275 patients were included in the study: 58 (21.1%) patients received BSC, 184 (66.9%) received chemotherapy, and 33 (12.0%) received multimodality treatment. All of our patients were exposed to asbestos environmentally. Sociodemographic and clinical characteristics of the MPM patients regarding treatment types are presented in Table 1.

The mean age of the patients was 63.2 ± 11.2 years, and 129 (46.9%) of them were female. Most of the patients had epithelioid subtype and advanced stage disease. The mean age of the patients was different from each other in all three groups ($P < 0.001$). KPS was the highest in the multimodality group and the lowest in the BSC group ($P < 0.001$) [Table 1]. The median cost per patients and median survival of the MPM patients regarding sociodemographic and clinical characteristics are presented in Table 2.

Table 1: Sociodemographic and clinical characteristics of the patients with malignant pleural mesothelioma by treatment types

Variables	Total (*n*=275)	BSC (*n*=58)	Chemotherapy (*n*=184)	Multimodality treatment (*n*=33)	*P*
Age (years)					
Mean±SD	63.2±11.2	71.5±8.7	62.3±10.6	53.6±9.0	<0.001
Range	28-87	50-87	28-81	34-70	
Gender *n* (%)					
Male	146 (53.1)	26 (44.8)	101 (54.9)	19 (57.6)	0.351
Female	129 (46.9)	32 (55.2)	83 (45.1)	14 (42.4)	
Histology *n* (%)					
Epithelioid	205 (74.5)	38 (65.5)	141 (76.6)	26 (78.8)	0.199
Nonepithelioid	70 (25.5)	20 (34.5)	43 (23.4)	7 (21.2)	
Stage* *n* (%)					
1-2	50 (18.5)	11 (20.0)	30 (16.4)	9 (27.3)	0.315
3-4	221 (81.5)	44 (80.0)	153 (83.6)	24 (72.7)	
KPS *n* (%)					
≤70	55 (20.0)	34 (58.6)	21 (11.4)	0	<0.001
>70	220 (80.0)	24 (41.4)	163 (88.6)	33 (100.0)	

*Four patients were not staged. BSC: Best supportive care, SD: Standard deviation, KPS: Karnofsky Performance Status

The median survival time ± standard deviation of patients was 10.0 ± 0.785 months in the study. Patients with <65 years old, epithelioid type, and >70 KPS had a longer survival time compared to patients with ≥65 years old, nonepithelioid type, and KPS ≤70, but the cost was higher. Patients with early-stage disease had longer survival time than those with advanced stage disease but did not differ in terms of cost.

The impact on survival and cost of each of the three treatment modalities were different from each other. The total median costs per patient and median survivals were $1838 and 5 months, $10,540 and 11 months, and $17,022 and 22 months for the BSC group, the chemotherapy group, and the multimodality group, respectively. Multimodal treatment was the most expensive treatment type with the longest duration of survival, whereas BSC was the cheapest treatment type with the shortest survival time. There was no difference among treatment groups in terms of diagnosis phase cost ($1397 for BSC group, $1457 for chemotherapy group, and $1564 for multimodality group) (P = 0.685). The terminal phase costs were similar for chemotherapy and multimodality groups ($328 vs. $377). Cost difference between the groups was due to the treatment expenditures in the active treatment phase.

The difference in median survival and median incremental costs per month gained of the MPM patients regarding treatment types are presented in Table 3.

The median survivals of the chemotherapy and multimodality groups were 6 and 17 months longer than that of the BSC group, respectively. The median incremental costs per month gained were $1451 and $893 in the chemotherapy and multimodality groups compared to the BSC group, respectively. The median survival of the multimodality group was 11 months longer than that of the chemotherapy group. The median incremental cost per month gained was $589 in the multimodality group compared to the chemotherapy group [Table 3]. The factors affecting the cost of the MPM patients are presented in Table 4.

Factors affecting the cost of MPM were histology, treatment type, received second- and third-line chemotherapy, and number of hospitalization. The cost was higher among patients who had epithelioid

Table 2: The median cost per patients and median survival of the patients with malignant pleural mesothelioma by sociodemographic and clinical characteristics

	Median cost per patient (IQR) ($)	*P*	Median survival time (months), 95% CI	*P*
Age				
<65	11,527 (7624-15,857)	<0.001	12.0 (9.3-14.7)	0.030
≥65	6666 (2478-11,795)		10.0 (8.0-12.0)	
Gender				
Male	8616 (5080-13,903)	0.903	9.0 (7.6-10.5)	0.110
Female	9796 (3590-14,702)		12.0 (9.3-14.7)	
Histology				
Epithelioid	10,600 (5065-15,207)	0.001	13.0 (10.9-15.1)	<0.001
Nonepithelioid	7595 (2840-10,324)		6.0 (4.4-7.6)	
Stage				
I-II	10,413 (4474-17,715)	0.235	17.0 (14.1-20.0)	0.003
III-IV	8921 (4707-13,771)		9.0 (7.5-10.5)	
KPS				
≤70	2990 (1680-6686)	<0.001	3.0 (1.6-4.5)	<0.001
>70	10,688 (6910-15,001)		12.0 (10.3-13.7)	
Treatment				
BSC	1838 (1255-2657)	<0.001	5.0 (3.4-6.6)	<0.001
Chemotherapy	10,540 (7413-14,350)		11.0 (9.4-12.6)	
Multimodality treatment	17,022 (12,420-22,377)		22.0 (13.5-30.5)	
Total	3016 (2234-4531)		10.0 (8.5-11.5)	

BSC: Best supportive care, KPS: Karnofsky Performance Status, CI: Confidence interval, IQR: Interquartile range

Table 3: Comparison of treatment types regarding cost and median survival

Treatment type	Difference in median survival between treatment types (months)	Incremental cost per month gained ($)
BSC versus chemotherapy	6 (Log-rank: 27.807; *P*<0.001)	1451
BSC versus multimodality treatment	17 (Log-rank: 27.738; *P*<0.001)	893
Chemotherapy versus multimodality treatment	11 (Log-rank: 5.999; *P*=0.014)	589

BSC: Best supportive care

Table 4: Factors affecting the cost of the patients with malignant pleural mesothelioma

	Unstandardized β	Standardized β	95% CI	*P*
Age	−0.052	−0.067	−0.118-0.013	0.118
KPS	0.015	0.016	−0.067-0.098	0.710
Comorbidity	0.014	0.019	−0.047-0.076	0.645
Histology	−0.070	−0.080	−0.137-−0.003	0.042
Stage	0.012	0.012	−0.066-0.090	0.763
Treatment	0.443	0.630	0.378-0.509	<0.001
Second-line chemotherapy	0.089	0.108	0.010-0.167	0.027
Third-line chemotherapy	0.168	0.134	0.059-0.277	0.003
Hospitalization number	0.038	0.117	0.011-0.065	0.006
Death at hospital	−0.009	−0.009	−0.092-0.074	0.825
Regression model		F=45.573; P<0.001, R^2=0.653		

CI: Confidence interval, KPS: Karnofsky Performance Status

histology, received treatment, received second- and third-line chemotherapy, and had higher hospitalization number than those who had nonepithelioid histology, received BSC, did not receive second- or third-line chemotherapy, and had lower hospitalization number.

Discussion

Since the incidence of MPM is expected to increase, the economic burden is also likely to increase. The economic burden of mesothelioma attributable to occupational asbestos exposure was assessed in various studies.[14-16] These studies reported the huge economic burden related to mesothelioma. Tompa *et al*. from Canada evaluated direct, indirect, and quality of life cost related to mesothelioma in 427 mesothelioma cases diagnosed in 2011. The key components were health-care costs, productivity and output costs, and quality of life costs. They found that the total society burden of mesothelioma was $C1 130 398 per case with direct and indirect costs comprising 39% and quality of life costs 61%. Total health-care costs were $C54 393 per case. The biggest impact was on loss of quality of life.[14] Another study from Italy analyzed two main cost groups, public costs including medical care costs, insurance, tax and benefits, and social costs.[15] They estimated a total cost of almost €250,000 for each mesothelioma case. The highest amount was on loss of productivity. The costs for medical care were €33,000 in their study. Hence, the cost can be different between the countries and their insurance systems and should be adjusted for comparison with each other.

There are no data about the costs of mesothelioma attributable to environmental asbestos exposure. In this study, we were able to evaluate only direct medical costs for patients with MPM followed up from hospital application date to death. Total median costs per patient were $3016. Total median costs in chemotherapy and multimodality groups were approximately six and nine times higher than BSC group. Health-care expenditures in our country are very low compared to western countries because of exchange rate differences. There was no difference between the treatment groups, chemotherapy and multimodality treatment groups, in terms of diagnosis and terminal phase costs. However, in the active treatment groups, chemotherapy and multimodality, as the survival rate increased, the total costs also increased. In other words, the survival of selected patient groups can be prolonged by aggressive treatment, i.e., chemotherapy/multimodality treatment and second/third-line chemotherapy, but the prolongation of survival is costly. The median cost of BSC group was the lowest, but the median survival time was significantly shorter than the other two groups. These results suggest that antitumor treatments can be performed even though to be costly because of the increased survival by treatment in selected patient groups with good prognostic factors and hence may be considered as cost-effective. Otherwise, it could be considered that expensive applications, particularly surgical applications, may not be performed in patients who are not expected to respond to treatment. Epithelioid type of mesothelioma has a good prognosis and its treatment response is well.[11] In this study, the costs were higher in patients with epithelioid histology than nonepithelioid as expected.

Pemetrexed has been the standard of choice in almost the entire world in the first-line chemotherapy of mesothelioma since 2003.[7] Another antifolate agent raltitrexed that has similar efficacy to pemetrexed can also be considered to reduce the cost related to treatment.[17] Woods *et al*. showed that raltitrexed plus cisplatin was cost-effective compared with pemetrexed plus cisplatin in MPM.[18] We evaluated that only chemotherapy regimen included pemetrexed in this study. However, in our previous study, pemetrexed plus platinum was not superior to gemcitabine plus platinum in MPM.[19] We did not analyze separately in the current study, but RT could be another application that could increase costs in mesothelioma. Therefore, RT may not be administered

if it is not a part of multimodality therapy or if pain palliation is not required. In SMART trial, routine use of prophylactic RT in all patients with mesothelioma after large-bore thoracic interventions was not justified and cost-effective.[20,21] Another factor that increased the costs was the hospitalization number in this study. In our unit, chemotherapy is performed remotely; hospital admissions in the process are due to complications of treatment or palliation of symptoms. Intensive care unit follow-ups may also increase the costs of patients who do not have an additional recoverable problem other than mesothelioma in their terminal phase. We were not able to evaluate the costs of intensive care unit because of insufficient number of patients treated in this unit. Nevertheless, we observed that the costs of some patients who admitted to the intensive care unit in the terminal phase were increasing up to ten times compared to others. For this reason, we do not recommend the intensive care unit for terminally ill patients without a reversible clinical problem such as pulmonary embolism and pneumonia.

Compensation is another important issue and sometimes can reach huge quantities, especially in mesothelioma patients with occupational asbestos exposure.[14,15,22] However, it is important that strategies should focus on decreasing underreporting of compensable mesothelioma. In Alberta, only 40% of cases filed a claim and 80% of them were accepted for compensation.[23] All of the patients in our study groups were exposed to asbestos environmentally, and the male/female ratios were similar. Most of our study population were farmers and homemakers. Thus, we have not been able to make an assessment of the compensation. However, since the Turkey National Mesothelioma Surveillance has informed government authorities about villages using asbestos-contaminated soil, necessary measures must be taken to rehabilitate these villages to prevent future cases.[24]

There are some limitations of this study. First, this is a retrospective study. Second, only direct costs were calculated from the computer-based patient registration system. Moreover, the billing of health-care services in our country is very cheap compared to western countries.[14-16] Then, adjustments are necessary to better understand the cost of mesothelioma. Therefore, we presented the prices of some health-care applications for January 2018 in Turkey [Supplementary Table 1]. Our data cannot be compared with western countries, but it can be a guide for the developing countries where the incidence of mesothelioma is increasing.

Conclusion

MPM has a limited survival time despite treatment, and treatment cost is relatively high by prolongation of lifetime. Treatment applications should be given to selected patients with good prognostic factors. Chemotherapy and multimodality approaches seem to be cost-effective until to be find more effective targeted therapies. It is clear that there is a need of well-designed prospective studies for cost analysis of MPM.

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Conflicts of interest

There are no conflicts of interest.

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