

## RESEARCH ARTICLE

# Clinicopathological Features of Patients with Malignant Mesothelioma in a Multicenter, Case-Control Study: No Role for ABO-Rh Blood Groups

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### Abstract

**Background:** Malignant mesothelioma (MM) is an aggressive tumor of mesothelial surfaces. Previous studies have observed an association between ABO blood groups and risk of certain malignancies, including pancreatic and gastric cancer; however, no information on any association with MM risk is available. The aim of this study was to investigate possible associations among MM clinicopathological features and ABO blood groups and Rh factor. **Materials and Methods:** In 252 patients with MM, the ABO blood group and Rh factor were examined and compared with the control group of 3,022,883 healthy volunteer blood donors of Turkish Red Crescent between 2004 and 2011. The relationship of blood groups with various clinicopathological features were also evaluated in the patient group. **Results:** The median age was 55 (range: 27-86) and 61.5% of patients were male. While 82.8% of patients had a history of exposure to asbestos, 60.7% of patients had a smoking history. Epithelioid (65.1%) was the most common histology and 18.7% of patients had mixed histology. Overall, the ABO blood group distribution of the 252 patients with MM was comparable with the general population. The median overall survival (OS) was 14 months (95% confidence interval, 11.3-16.6 months). The median OS for A, B, AB, and O were 11, 15, 16, and 15 months respectively ( $p=0.396$ ). First line chemotherapy was administered to 118 patients. The median OS of patients on pemetrexed or gemcitabine was longer than patient who was not administered chemotherapy [17 months (95% CI, 11.7-22.2) vs. 9 months (95% CI, 6.9-11.0);  $p<0.001$ ]. **Conclusions:** The results of this study suggest that patients with MM can benefit from treatment with pemetrexed or gemcitabine in combination with cisplatin. We did not observe a statistically significant association between ABO blood group and risk of MM.

**Keywords:** Mesothelioma - blood groups - asbestos

*Asian Pacific J Cancer Prev*, 14 (1), 249-253

### Introduction

Malignant mesothelioma (MM) is aggressive tumor of serosal cavities which refractory to conventional therapies. The frequency is increasing worldwide. For a long time it has been known that the people of certain region of Turkey, especially villages in rural Cappadocia, suffer from MM and approximately 50% of all deaths due to MM (Baris et al., 1978; Roushdy-Hammady et al., 2001; Emri et al., 2002; Carbone et al., 2011). The most important risk factor for MM is exposure to asbestos and erionite (non-asbestos mineral; fibrous zeolite) (Emri et al., 2002; Lee et al., 2009; Carbone et al., 2011). The role of environmental factor has been studied since 1970's in Turkey (Baris

et al., 1978; Metintas et al., 2002). It was reported that asbestos exposure rate was 50-80% (Tanrikulu et al., 2010; Elkiran et al., 2012). However, not all type of asbestos is equally carcinogen and type and size of asbestos fiber are important determinant of potency. It was suggested that amphibole asbestos is more potent than chrysotile toward the induction of MM and thinner and longer fibers are more carcinogenic (Berman and Crump, 2008; Heintz et al., 2010). Nevertheless, approximately 20% of MM occurs in individuals without a history of asbestos exposure, and less than 10% of people heavily exposed to asbestos will develop MM. Therefore, additional factors may contribute to the development of MM. Although the data about simian virus 40 (SV40) are controversial

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it is suggested as one potential co-factor (De Rienzo et al., 2002). The role of genetic factors in the development of cancer is widely accepted. Roushdy-Hammady et al. (2001) and Dogan et al. (2006) suggested that a genetic factor, especially for sporadic MM in more developed countries, may be responsible for the development of MM. Pedigree and mineralogical studies indicate that the MM epidemic is caused by erionite exposure in genetically predisposed individuals (Roushdy-Hammady et al., 2001; Dogan et al., 2006).

The diagnosis of MM can be difficult and despite repeated cytological and radiological examination, diagnosis may not be confirmed. Histopathologic evaluation still is a gold standard for diagnosis of MM. Although some marker may have, diagnostic and prognostic role but limited data are available (Husain et al., 2009; Kao et al., 2011; Tischoff et al., 2011; van der Bij et al., 2011).

Optimal treatment of MM still is investigated. Radical surgery is appropriate for minority of patients. Although multimodal treatment is suggested for those patients, the results are controversial (Stahel et al., 2010; Treasure et al., 2011; van Meerbeeck et al., 2011; Rusch et al., 2012). For those patients who are not candidate for curative resection, platinum based treatment such as pemetrexed or gemcitabine combined with platinum are treatment of choice (Vogelzang et al., 2003; Utkan et al., 2006; Elkiran et al., 2012).

In 1953 Aird et al. reported a relation between blood group A and cancer of the stomach (Aird et al., 1953). Recently the relation between pancreatic cancer and ABO blood group has been described (Wolpin et al., 2009; Iodice et al., 2010; Engin et al., 2012). ABO blood group genes are mapped at the chromosome 9q, in which the genetic alteration is common in many cancers. Previously, some studies have been found that blood group antigens may be helpful for differential diagnosis of MM and adenocarcinoma of lung (Jordon et al., 1989; Noguchi et al., 1989). However it is unknown whether there is a relationship between ABO blood groups, MM, and clinicopathological features or not.

The aim of this study is to investigate the presence of a possible association between MM, and clinicopathological features and ABO blood groups and Rh factor.

## Materials and Methods

All patients who had pathologically confirmed diagnosis of MM and treated between 2000-2011 at the Departments of Medical Oncology and Thoracic Surgery of Ankara University School of Medicine, Department of Thoracic Surgery of Başkent University School of Medicine, Medical Oncology Clinics of Ankara Numune Research and Educational Hospital and Dr. Abdurrahman Yurtaslan Research and Educational Hospital (Ankara, Turkey) and Süleyman Demirel University School of Medicine, Department of Medical Oncology (Isparta, Turkey) with serologically confirmed ABO blood type and Rh factor were included in our retrospective reviews of tumor registry records. We excluded patient with a history of other cancer. A group of volunteer healthy

donors of Turkish Red Crescent (General Directorate of Blood Services, Science and Technological Research Directorate) between 01.01.2004 and 27.10.2011 were identified as a control group. The relationship of ABO blood types and Rh factor with various factors such as age at diagnosis, sex, history of asbest exposure, smoking, histology, stage, and overall survival (OS) were evaluated from 252 MM patients. Patients classified according to antigen status as follow; O (blood group O) and nonO (group A, B, and AB); A (group A and AB) and nonA (group B and O); B (group B and AB) and nonB (group A and O). We compared the distributions of ABO blood types (A vs. nonA, B vs. nonB, O vs. nonO), Rh factors (positive vs. negative) among 252 patients and 3,022,883 healthy controls. Among MM patients, differences between each of aforementioned ABO blood groups and Rh factors with respect to various factors were explored, respectively.

This study was approved by the institutional medical ethics review board and conducted according to Helsinki Declaration and good clinical practice.

Statistical analysis was carried out using the computer program Statistical Package for the Social Sciences 13.0 for Windows (SPSS, Inc, Chicago, IL, USA). Descriptive statistics as frequency (percent) or median (minimum-maximum) were calculated for all variables. A  $\chi^2$  test was used to detect statistical differences in proportions. Odds ratio and its confidence interval were also calculated. OS is defined as the time from diagnosis until death from any cause or last follow-up and was calculated according to Kaplan-Meier, and the differences between groups were analyzed using the log-rank statistics (Kaplan and Meier, 1958; Peto et al., 1977). All tests were two-tailed and a p value of less than 0.05 was considered significant.

## Results

Among patients; the median age was 55 (range: 27-86) and 61.5% of patients were male. While 82.8% of patients had a history of exposure to asbestos; 60.7% of patients had a smoking history (Table 1).

Overall distributions of ABO blood groups as well as Rh factor were comparable between patients and controls. There was not statistically significant difference ( $p=0.86$ ) between groups (Table 2 and 3). As well, there were not statistically significant difference between patients and controls with respect to O vs. non O, A vs. non A, and B vs. non B blood group. In addition, the distribution of ABO blood group and Rh factor were similar regarding to gender, histologic subtype, asbestos exposure, smoking history, and stage.

The median overall survival (OS) was 14 months (95% confidence interval, 11.3-16.6 months). The median OS for A, B, AB, and O were 11, 15, 16, and 15 months respectively. Although median OS for group A was shorter than other groups, this difference was not statistically significant ( $p=0.396$ ). Trimodality treatment was performed for 17 patients. Even though, the OS for those patients was longer than others, the difference was not statistically significant (15 vs. 13 months,  $p=0.103$ ). First line chemotherapy was administered to 118 patients. Median OS was 17 (95%CI, 8.7-25.2) months in the

**Table 1. Patients' Characteristics**

Sex (male, %)		61.5%
Age at diagnosis, median (range), year		55 (27-86)
Smoking history, %	60.7%	
Asbestos exposure, %	82.8%	
Histological subtype,%	Epithelioid	65.1%
	Sarcomatoid	5.2%
	Mixt	18.7%
	Unknown	11.1%
Surgery	Pleurectomy/decortications	30.0%
	EPP	3.8%
	VATS	48.3%
	Other <sup>1</sup>	18.9%
Stage	I	38.1%
	II	19.8%
	III	17.9%
	IV	6.3%
	Unknown	17.9%
RT, %		19.0%
First line CT (n=118), %	Cisplatin-pemetrexed	45.0%
	Cisplatin-gemcitabine	37.0%
	Platinum-taxan	6.0%
	Other <sup>2</sup>	12.0%
Second line CT,%	Cisplatin-pemetrexed	2.5%
	Cisplatin-gemcitabine	1.0%
Median OS, months		14 (95%CI, 11.3-16.6)

\*VATS: Video-assisted thoracic surgery, EPP: extrapleural pneumonectomy, <sup>1</sup>resection of chest wall, pleuroperitoneal shunt, pleurodesis, minithoracotomy-biopsi, <sup>2</sup>ifosfamide, interferon, single agent pemetrexed, single agent gemcitabine

**Table 2. The Blood Group Distribution of Patients and Control Group**

	ABO blood group			
	A	B	AB	O
Mesothelioma*				
	104 (41.3)	45 (17.9)	21 (8.3)	82 (32.5)
Control group				
	1,276,032 (42.2)	493,769 (16.3)	229,554 (7.6)	1,023,528 (33.9)

\*P=0.868

**Table 3. The Rh Group Distribution of Patients and Control Group**

	Rh+		Rh-	
	n	(%)	n	(%)
Mesothelioma*				
	221	(87.7)	31	(12.3)
Control group	2,651,027	(87.7)	371,856	(12.3)

\*P=1.000

cisplatin- pemetrexed (49 patients) combination and 16 (95%CI, 10.4-21.5) months in the cisplatin – gemcitabine (39 patients) combination. There was no statistically significant difference regarding OS between the patients who received pemetrexed and gemcitabine. However, the median OS of patients on pemetrexed or gemcitabine was longer than patient who was not administered chemotherapy [17 months (95%CI, 11.7-22.2) vs. 9 months (95%CI, 6.9-11.0); p<0.001].

## Discussion

In this multicentric, case-control study, we did not find an association between ABO blood group and risk

of MM. In additionally, we did not observe significant associations between serologic ABO blood type and age, asbestos exposure, smoking history, histological subtype, stage, and OS.

The ABO blood group system was discovered by Karl Landsteiner. ABO blood groups are determined by carbohydrate moieties, A and B antigens, on the extracellular surface of the red blood cell membranes and anti-A or anti-B antibodies in the serum (Hosoi, 2008). However ABO antigens are also expressed on the surface of many other cells, like epithelial cells. Previous studies suggest a possible association between ABO blood group and the risk of some epithelial malignancies, including pancreatic cancer and gastric cancer (Aird et al., 1953; Wolpin et al., 2009; Iodice et al., 2010).

In study of Aird et al. more patients with gastric cancer had blood group A and less had blood group O than normal population (Aird et al., 1953). However, there was not statistically significant difference in study of Iodice et al. for distribution of blood group in patient with gastric cancer. Nonetheless in same study, significantly lower frequency of blood group O was observed in patient with exocrine pancreatic cancer (Iodice et al., 2010). Pancreatic cancer is one of the best-studied cancer respect to blood group relation with cancer. In addition, other studies have shown that relation of blood group with pancreatic cancer. The common features of these studies, nonO blood group has been associated with an increased risk of pancreatic cancer (Annese et al., 1990; Wolpin et al., 2009; Greer et al., 2010; Iodice et al., 2010; Ben et al., 2011; Nakao et al., 2011; Engin et al., 2012). Colorectal cancer is another gastrointestinal cancer that this issue has already been investigated. Khalili et al. (2011) were not observed a statistically association between ABO blood group and risk of colorectal cancer (Khalili et al., 2011). However, in our previous study, nonO blood group was associated with increased risk of colon adenocarcinoma (Urun et al., 2012).

MM occurs predominantly in men (ratio of men to women, 5/1), and risk increases with age (median age at diagnosis is 72 years in the United States; range, 45-85 years) (Tsao et al., 2009). In our study also MM predominantly reported in man but ratio of men to women was 3/2. Our patients were younger than the patients reported from US and in the present study median age was 55 (range: 27-86). In additionally in our study patient with smoking history were younger than patient without smoking history. The possible explanation for this difference is occupational asbestos exposure begins later age and median age for MM is 60-65 years. However environmental exposure start at birth and the median age is 50s (Metintas et al., 2002). The histological analyses of present study are consistent with literature and most observed subtype was epithelioid form (Husain et al., 2009; Tischoff et al., 2011; Rusch et al., 2012). The median OS was 14 months. Platinum-based combination chemotherapy was related with longer OS. However, there was not statistically significant difference between pemetrexed and gemcitabine.

This study has several limitations. First, case control studies are retrospective and observational in nature and

subject to bias. Second, we include patients, whose ABO blood group information was available. Third, despite a large control group, the numbers of MM cases were limited, especially in some blood groups. The strengths of this study; first the ABO blood group was serologically confirmed. Second, diagnosis of MM was pathologically confirmed. To our knowledge, this is the first study investigating the association between the ABO blood group and MM risk.

In summary, the results of this study suggest that patients with MM can benefit from treatment with pemetrexed or gemcitabine in combination with cisplatin. We did not observe relationship between MM, clinicopathological features of MM and ABO blood group and Rh factor. However further studies with larger number of patients are needed to establish the role of blood groups in this population.

## Acknowledgements

We are indebted to Armağan Aksoy, M.D. and the Turkish Red Crescent (Türk Kızılayı [General Directorate of Blood Services, Science & Technological Research Directorate]) and Önder Arslan, M.D. and Ankara University Medical School Blood Center for their help. Conflict of interest, the authors declared that there are no potential conflicts of interest, neither financial nor of other nature, to disclose.

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