RESEARCH ARTICLE

ABO Blood Groups are Not Associated with Treatment Response and Prognosis in Patients with Local Advanced Non-Small Cell Lung Cancer

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Abstract

Background: Lung cancer is the leading cause of cancer death, late diagnosis being the main obstacle to improving the outcomes with stage at diagnosis as an important prognostic factor. Relationships between ABO blood groups and risk of benign or malignant diseases have been observed and in this study, we aimed to investigate whether they might affect prognosis and response to chemoradiotherapy in patients with local advanced non-small cell lung cancer (NSCLC). Materials and Methods: Eighty-one patients with non-metastatic local advanced NSCLC were included in the study. ABO blood groups were A in 45 (55.6%), B in 7 (8.6%), AB in 8 (9.9%), and O in 21 (25.9%) patients. The patients were also divided two groups according to blood group A (45 patients) and non-A (B, AB and O; 36 patients). Response to chemoradiotherapy was complete remission in 10 (12.3%), disease regression in 42 (51.9%), stable disease in 12 (14.8%), and disease progression in 17 (21.0%) patients. Results: There was no significant difference among ABO blood group categories or between patients with A blood group and those with non-A blood group in terms of responses to chemoradiotherapy (p>0.05). There were also no significant differences regarding overall and disease-free survival rates. Conclusion: The ABO blood group system has no significant effect on prognosis and response to chemoradiotherapy in patients with non-metastatic NSCLC.

Keywords: ABO blood groups - lung cancer - prognosis - response to chemoradiotherapy

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Introduction

Lung cancer is the leading cause of cancer deaths. Much of the cases are at the advanced stage on diagnosis, so late diagnosis is still an obstacle to improving the outcomes in this malignancy and early stage at diagnosis is an important prognostic factor (Finkelstein et al., 1986).

As screening and early diagnosis have been shown to increase survival in some solid tumors as breast, colon and cervix and since localized lung cancer can be managed curatively; it is believed that lung cancer is an appropriate candidate for population based screening programs. In National Lung Screening Trial (NLST), it has been shown that screening high risk patients with low-dose helical CT decreases the mortality rate from lung cancer by 20% compared to chest x-ray. In that study, high risk patients were 55-74 years old and current of former smokers with a 30 pack-year smoking history (Aberle et al., 2011). So it is important to define the high risk group patients for early diagnosis and chance of cure.

The ABO blood group system was first discovered by Karl Landsteiner, who found three different blood types (A, B, and O) in 1900 (Landsteiner, 1900). Blood group antigens are chemical components on membrane of the red blood cells but they are also expressed on a variety of epithelial cells including urothelium, gastrointestinal, mucosa and lung as well as saliva and body fluids (Zmijewski, 1978; Graziano et al., 1997). ABO blood group genes are mapped at the chromosome 9q and consist of 7 exons, in which the genetic alteration is common in many cancers (Hosoi, 2008). Blood group antigens have an important role in identifying matched blood products for transfusion.

It has been reported that some of these molecules have varied and important functions in cell physiology and human pathology (Mohandas and Narla, 2005). The relationships between ABO blood groups and benign or malignant diseases have been observed for a long time. Deficiency of these membrane components is related to certain erythrocytes disorders (Mohandas and Narla,

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2005). Aird et al. (1953) reported such a relationship with gastric cancer. They have found that blood group A was significantly more frequent, while blood group O was less frequent in patients with gastric cancer when compared with normal population in England (Aird et al., 1953). Recently in some studies, a significant association between ABO blood groups and the risk of certain malignancies, including pancreas cancer, colorectal cancer, ovarian cancer, and acute myeloid leukemia has been reported (Wolpin et al., 2009; Greer et al., 2010; Modak et al., 2011; Urun et al., 2012; Yuzhalin and Kutikhin, 2012).

In this study, we aimed to investigate whether ABO blood group system has effect on the prognosis and response to chemoradiotherapy in patients with local advanced non-small cell lung cancer (NSCLC).

Materials and Methods

Eighty-one patients with non-metastatic NSCLC were included in the study. We recorded blood group, responses to chemoradiotherapy including complete remission, regression, stable disease, and disease progression, and overall and disease-free survival. Survival time was measured from the date of chemoradiotherapy until death or last clinical evaluation.

Patients were excluded if they were <18 years old, had severe disease such as heart failure and hepatic failure, had a history of any other cancer, or had a metastatic disease.

Histopathology of NSCLC was epidermoid carcinoma in 50 (61.7%), adenocarcinoma in 17 (21.0%), pleomorphic carcinoma in 1 (1.1%), adenosquamous carcinoma in 1 (1.1%), and unclassified non-small cell lung cancer in 12 (14.8%) patients. The stage of the lung cancer was IIA in 2 (2.5%), IIB in 4 (4.9%), IIIA in 37 (45.7%), and IIIB in 38 (46.9%) patients.

ABO blood group was A in 45 (55.6%), B in 7 (8.6%), AB in 8 (9.9%), and O in 21 (25.9%) patients. The patients were also divided two groups according to blood group A (45 patients) and non-A (B, AB and O; 36 patients).

Radiotherapy and chemotherapy

Two-dimensional radiotherapy treatment planning system was used. Total dose to the involved areas was 66 Gy in 33 fractions of 2 Gy each, for 5 days a week given over a period of 6.5 weeks. During radiotherapy concomitantly weekly docetaxel 20 mg/m^2 and cisplatin 20 mg/m^2 infusion were administered.

Response to chemoradiotherapy was complete remission in 10 (12.3%), disease regression in 42 (51.9%), stable disease in 12 (14.8%), and disease progression in 17 (21.0%) patients (RECIST 1.0 was used for response evaluation).

Statistical analysis

SPSS 15.0 software was used for the statistical analysis. Continuous variables with normal distribution were presented as mean±SD. Qualitative variables are given as percent and the correlation between categorical variables was investigated using the chi-square test and Fisher's exact tests. Disease-free survival and overall survival was estimated using the Kaplan-Meier method and the log-rank test was used for comparison of outcomes. A p value of <0.05 was considered significant.

Results

Mean age was 58.4±7.8 (30-78) years. 74 (91.4%) of the patients were male, the rest were female.

Table 1 shows responses to chemoradiotherapy according to blood group categories. There was no significant difference among ABO blood group categories in terms of responses to chemoradiotherapy (p>0.05). Similarly, there was no significant difference between patients with A blood group and those with non-A blood group in terms of responses to chemoradiotherapy (p>0.05).

Overall and disease-free survivals were 15 and 9 months, respectively (Figure 1).

Table 2 shows survival rates according to blood group categories. There was no significant difference when the overall and disease-free survival rates of the patients were compared according to the ABO blood groups (p>0.05). Similarly, there was no significant difference between patients with A blood group and those with non-A blood group in terms of the overall and disease-free survival rates (p>0.05).

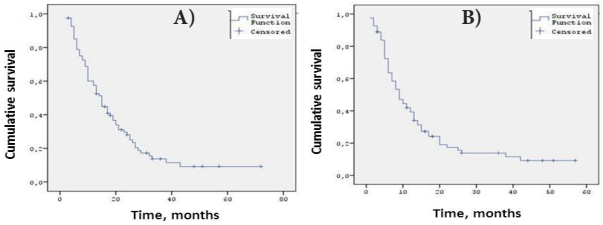

Figure 1. A) Overall and B) Disease-Free Survivals were 15 and 9 Months, Respectively

Table 1. Responses to Chemoradiotherapy According to Blood Group Categories

	Complete response n (%)	Disease regression n (%)	Stable disease n (%)	Disease progression n (%)	P value
ABO blood groups					0.284
A	4 (40)	21 (50)	7 (58.3)	13 (76.5)	
B	1 (10)	3 (7.1)	3 (25)	-	
AB	1 (10)	5 (11.9)	1 (12.5)	1 (05.9)	
O	4 (40)	13 (31)	1 (12.5)	3 (17.6)	
Total, n (%)	10 (100)	42 (100)	12 (100)	17 (100)	
A vs. non-A blood groups					0.208
A	4 (40)	21 (50)	7 (58.3)	13 (76.5)	
Non-A	6 (60)	21 (50)	5 (41.7)	4 (23.5)	

Table 2. Survivals and P-value According to Blood Group Categories

	No. of patients (%)	Overall survival months (95%CI)	P value	Disease-free survival months (95%CI)	P value
ABO blood groups			0.690		0.645
A	45 (55.6)	15 (12.50-17.50)		8 (5.26-10.74)	
B	7 (8.6)	12 (6.87-17.13)		10 (3.58-16.42)	
AB	8 (9.9)	13 (6.07-19.93)		7 (0-15.32)	
O	21 (25.9)	17 (5.04-28.96)		9 (7.89-10.11)	
A vs. non-A blood groups			0.910		0.861
A	45 (55.6)	15 (12.50-17.50)		8 (5.26-10.74)	
Non-A	36 (44.6)	13 (8.60-17.40)		9 (7.04-10.96)	

Discussion

ABO blood group system is the most important among 29 blood group system (Hosoi, 2008). Blood group antigens have an important role in identifying matched blood products for transfusion. In addition, they have many novel functions, including contributing to erythrocyte membrane structural integrity, transport of molecules through the membrane, complement regulation, and acting as adhesion molecules, receptors for extracellular ligands, and enzymes (Mohandas and Narla, 2005). Alterations in the inflammatory state caused by ABO blood group system may explain the relationship between ABO blood system and cancer risk (Wolpin et al., 2009). Influences of blood group antigens on inflammation processes have been evaluated in recent studies. Two studies have been found an association between single nucleotide polymorphisms at ABO blood group locus and inflammation (Melzer et al., 2008; Paré et al., 2008). Melzer et al. (2008) have identified a polymorphism close to the ABO blood group gene, which was very strongly associated with serum tumor necrosis factor-alpha levels (Melzer et al., 2008). Pare et al. have found that a single nucleotide polymorphism at the ABO (9q34.2) locus is highly correlated with soluble intercellular adhesion molecule 1 (sICAM-1) concentrations and suggest the novel association at the ABO locus provides evidence for a previously unknown regulatory role of histo-blood group antigens in inflammatory adhesion processes (Paré et al., 2008).

The role of inflammation in the lung cancer has been examined in various studies. Secretory phospholipase A2 (sPLA2) plays an important role in mediating the inflammatory signals that induce ICAM-1 expression in lung cancer cells. Invasive lung tumors are associated with ICAM-1 expression and up-regulation of PLA2 activity can enhance metastasis. Antibody blockade of ICAM-1 decreases lung cancer cell invasion and sPLA2 inhibition reduces ICAM-1 expression and invasion (Yu et al., 2012). Qian et al. have evaluated that the effects of vascular endothelial growth factor and sICAM-1 on patient survival and pleural effusion control in patients with lung adenocarcinoma with malignant pleural effusion (Qian et al., 2012). They found that the levels of VEGF and sICAM-1 in both pleural effusion and serum were significantly higher in patients with lung adenocarcinoma compared to patients with tuberculosis and that serum level of sICAM-1 was an independent prognostic factor for survival (Qian et al., 2012). These findings raise the possibility that blood group antigens may alter the systemic inflammatory response and thus suggest a possible mechanism to explain the association between blood type and cancer risk (Wolpin et al., 2009).

Several studies have been conducted to evaluate the relationship between ABO blood group and prognosis in cancer patients in our country, Turkey. Engin et al observed that blood group O had a significantly longer survival compared to non-O, regardless of prognostic factors in patients with pancreatic cancer (Engin et al., 2012). Kos et al. (2012) found that blood group A was a negative prognostic factor in 50 patients with pancreas cancer. The median overall survival in patients with blood group A was significantly lower than those with non-A blood group, 7.6 months versus 29.0 months. They thought that the ethnicity might have a role on the prognosis. Utkan et al. (2013) evaluated whether there is an association among ABO blood group, cancer, and prognosis in malignant mesothelioma and did not observe a significant association between ABO blood group and risk of malignant mesothelioma. In addition, they found no significant relationship between ABO blood group and prognosis in the patient population (Utkan et al., 2013).

We investigated relationship between histological type of cancer and ABO blood group in patients with lung cancer and found that there was no significant difference between patients with lung cancer of either type and the control group in terms of distribution of ABO blood groups. There was also no relationship with NSLC histological subtypes (Oguz et al., 2013). The relationship between ABO blood groups and the prognosis in patients with NSCLC have been evaluated in different studies. Graziano et al investigated the prognostic significance of blood group antigen A loss in 262 patients with surgically resected stage I and II NSCLC. Using paraffin-embedded primary tumor, immunohistochemical stains for blood group antigen A were performed on 90 patients with blood type A or AB. The median overall and disease-free survival ratios were significantly lower in patients with primary tumor negative for blood group antigen A compared with those with antigen A-positive tumor (Graziano et al., 1997). They suggested that the loss of A antigen was a powerful negative predictor for survival in the subgroup of patients with group A or AB and blood group antigens may have an important role in defining invasiveness and potential for metastases. Similarly, in a study performed by Lee et al it has been found that expression of blood group antigen A in tumor cells is an important favorable prognostic factor in patients with NSCLC (Lee et al., 1991). Kuemmel et al evaluated that relationship between blood group-related antigen Lewis and the ABH blood groups and prognosis in resected NSCLC and found that blood group A and Lewis Y expression on tumor cells was independent predictor for improved survival after tumor resection (Kuemmel et al., 2007). In addition, León-Atance et al observed that the loss of expression of blood group antigen A has a negative prognostic value in patients with stage I NSCLC, especially in those with adenocarcinoma (León-Atance et al., 2012).

To the best your knowledge, the relationship between ABO blood groups and prognosis and response to chemoradiotherapy has not been investigated in local advanced NSCLC patients treated with the same chemoradiotherapy regimen at same stage. In this study, we investigated whether ABO blood group system has effect on the prognosis and response to chemoradiotherapy in local advanced NSCLC patients received the same chemoradiotherapy regimen at same stage. We found there was no significant difference among ABO blood group categories in terms of responses to chemoradiotherapy and the overall and disease-free survival rates. Similarly, there was no significant difference between patients with A blood group and those with non-A blood group in terms

of responses to chemoradiotherapy and the overall and disease-free survival rates.

In conclusion, ABO blood group system has no significant effect on prognosis and response to chemoradiotherapy in patients with non-metastatic NSCLC.

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